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14. ABSTRACT
This research project, in its fourth year, continues to contribute to the suite of instruments, models and data for describing soft biological tissues. Accomplishments include: our first publication of our techniques and results in a major biomechanics journal; the development of a useful and detailed model describing the poroviscous, hyperelastic character of tissues; development of inverse techniques for the extraction of the characteristic parameters from this model, using existing pathological breast tissue data as a data source; construction of a new large strain, moderate rate, high fidelity bench-top indentation system, improving on the variety of testing that can be performed; adding a 3-D ultrasound scanning apparatus to measure 3-D strain fields during indentation; developed new algorithms to measure the internal strain field from data with low signal to noise ratios. External collaborations have lead to analysis of the Truth Cube 2 results and comparison with additional techniques; construction of prototypes of in vivo high speed testing devices with MIT which will be used for abdominal organ tissues, and design of an instrument for the measurement of porcine brain tissues; and successful construction of a miniature force sensor that will be used on the laryngoscopic vocal tissue testing device.

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Introduction

Computer-based medical modeling and simulation offers the potential for a completely new way to learn medical care. The use of computers as human assistants for medical diagnosis and training will require new knowledge domains. The most fundamental among these is the digital characterization of biophysical properties of perfused organs obtained from *in vivo* measurements, accounting for tissue properties integral to the organ as well as boundary conditions which affect the organ's global behavior.

Our research program is designed to obtain measurements of living tissue–liver, spleen and kidney–from large animal models and to use this data to characterize non-linear behavior during large-scale deformations, as would be seen in clinical practice. We are designing instruments to measure tissue properties and then creating mathematical models to allow representation of these data in a computer simulation.

The fourth year of the research has yielded: the first publication of our experimental techniques and results in a major biomechanics journal; completing the development of a useful and detailed model for describing the poroviscous, hyperelastic character of the tissues of interest; development of inverse techniques for the extraction of the characteristic parameters from this model, using existing pathological breast tissue data as a data source; construction of a new large strain, moderate rate, high fidelity bench-top indentation system to greatly improve on the variety of testing that can be performed beyond the manual large deformation indenter of years 2 and 3; a combined indentation and 3-D ultrasound scanning apparatus to simultaneously apply known loads and deformations and determine the internal deformations to improve the uniqueness of the parameters extracted from the model (to obtain 3-D strain field information instead of just the 1-D force-displacement information we have collected in the past); developed new algorithms to measure the internal strain field from data with low signal to noise ratios.

Finally, our external collaborations have lead to analysis of the truth cube results that we obtained and significant further measurement and comparison between measurement techniques by our international collaborators; construction of prototypes of *in vivo* high speed testing devices developed in collaboration with MIT which will be used for abdominal organ tissues and design of an instrument for the measurement of porcine brain tissues; and successful construction of a miniature force sensor that will be used on the laryngoscopic vocal tissue testing device.

All work has been done according to institutional- and Defense Department-approved animal studies protocols.

Body

The following sections present our fourth year results organized according to the Statement of Work from our original research proposal. As was the case in previous years, in addition to the planned research, the results obtained have led to modifications in our research approach to take advantage of new opportunities and based on lessons learned. These will also be described in the following sections. The points in the original statement include:

- Refinement of whole organ testing *in vivo* with boundary conditions
- Refinement of FEM of whole organ measurements

- 6-dof robotic measurement of renal forces / torques *in situ* for boundary effects
- Optimization of FEM methods for real-time interactivity
- Possible human tissue measurements of tissue pre-resection (indentation and implanted devices)
- FEM modeling of possible human measurements

In addition to these items, the following were also commenced, accomplished or progressed in year four:

- External measurements and analysis of Truth Cube 2 silicone cylinders
- High rate abdominal tissue testing devices and low rate brain testing device development
- Completion of miniature force sensor for vocal tissue testing

Refinement of whole organ testing *in vivo* with boundary conditions

Revision to ex vivo *testing using perfusion system*

Our original expectations for performing *in vivo* tissue testing have changed significantly based on the successful development of our normo-thermic extracorporeal liver perfusion (NELP) system. Obtaining an accurate characterization of the mechanical response of soft tissues is a challenge. Ideally, mechanical testing would happen under conditions that allow the tissue to be in its natural state and allow for the tests to be done under completely controlled loading and boundary conditions. These scenarios would call for both *in vivo* and *ex vivo* testing respectively. In year two we developed the NELP apparatus in an attempt to allow us to make carefully controlled *ex vivo* experiments under near *in vivo* conditions. In year three we presented the results that compared testing using two different indentation devices across four conditions (*in vivo, ex vivo* perfused, *ex vivo* post perfused, and *ex vivo* on an excised section) suggesting that perfusion affects the viscoelastic response of liver (see Figure 1). The results stress the importance of accounting for both geometric and physiologic boundary conditions when characterizing well-vascularized, solid whole organs like the liver. Furthermore, this system permits us to harvest whole organs from the animal subject (post-sacrifice), return them to the laboratory and perform tests that yield data that closely approximate those made *in vivo*. The results of that work has been submitted to and accepted for publication in the Journal of Biomechanics [Kerdok et al., 2005a]. As a result of these findings, we have altered our approach to focus more on refinement of our bench-top techniques.

A new testing device has been constructed for the indentation tests on the liver. A high fidelity motorized linear actuator was purchased from Enduratec (ELF TestBench Series, EnduraTEC Systems Group, Minnetonka, MN) and adapted to indent liver tissues *ex vivo* using the perfusion apparatus. A new indenter head has been developed that allows the indenter to stick to the surface of the liver using suction. Large strain (~30% nominal strain) load/unload tests across various rates (0.25 to 10 Hz selected to cover the span of surgically relevant gestures) are being conducted to identify the parameters of the constitutive model (next section). Large strain (~30% nominal strain) stress relaxation and creep indentation studies are collected at

the same location as the ramp studies for validating the model. We plan to collect data on six porcine livers by the end of October (see Figure 2).

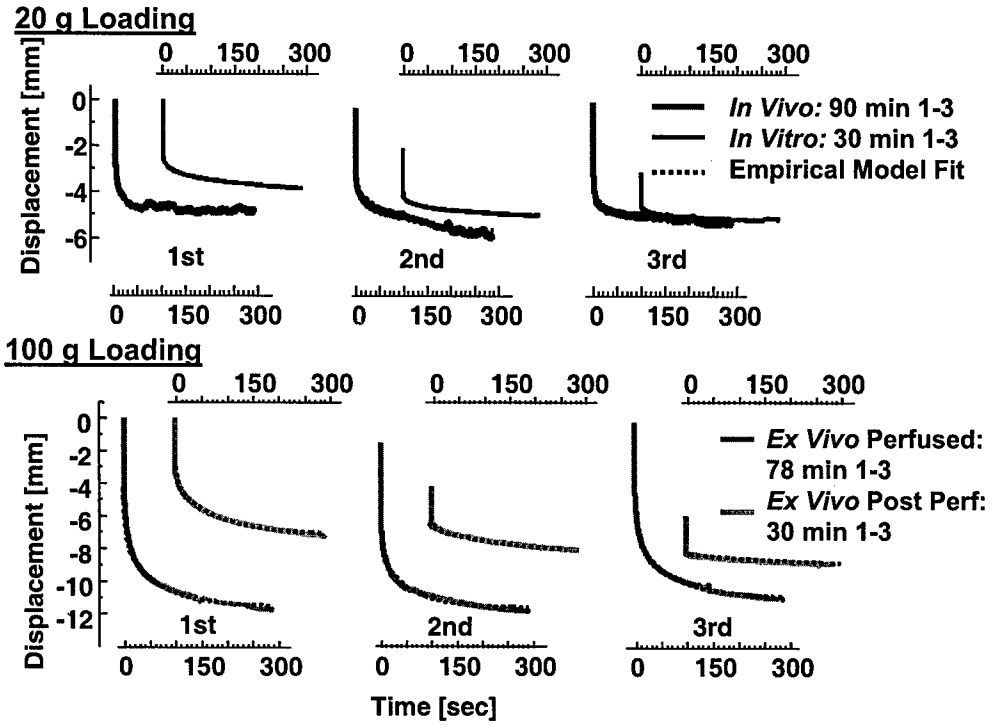

Figure 1: Large strain indentation results showing the effects of perfusion on the creep response of liver. Sequential indentations are shown to portray the consistency in the creep response for the perfused conditions, and the inconsistent response of the unperfused unperfused conditions. Empirical model fits to the data suggest that a 2 time-constant model is needed to capture the viscoelastic response.

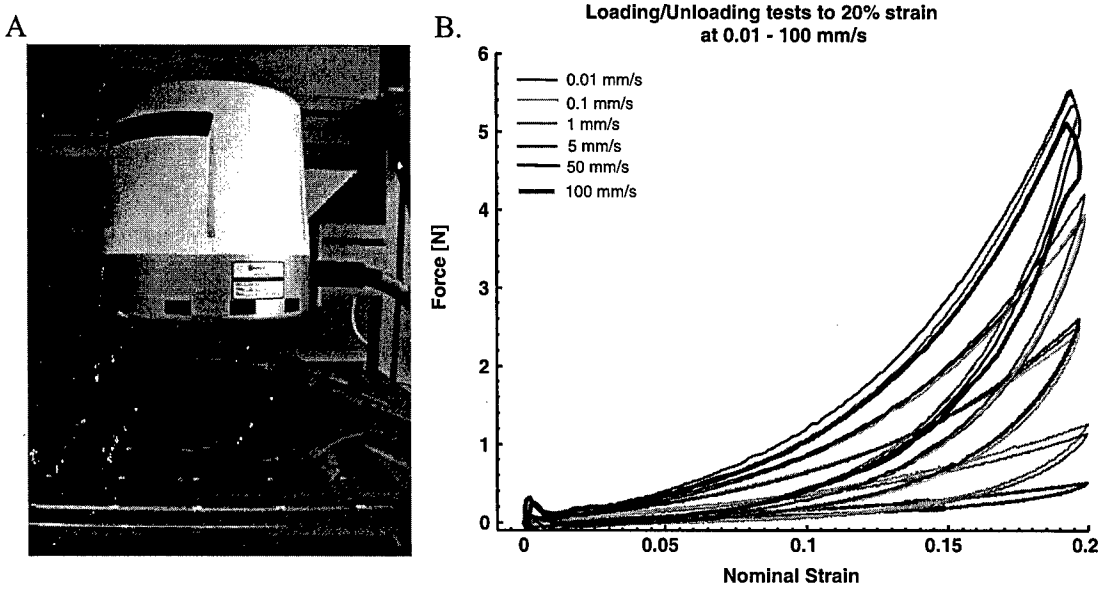

Figure 2: A) The Enduratec linear actuator indenting a perfused liver. B) Example of load/unload indentation study of perfused liver at a surgically relevant strain (~20%) and rates ranging from 0.01 to 100 mm/s.

We have further investigated the use of 3-D ultrasonic imaging in conjunction with large strain indentation, not only to control and understand the organ and indenter boundary conditions, but also to improve our ability to uniquely identify the organ-specific material parameters. Our previous work revealed relatively low parameter sensitivities (change in error function per change in parameter value) during the optimization process and raised the issue of uniqueness of model parameters. To address this issue we are developing a tissue characterization approach, which combines traditional indentation testing with three-dimensional ultrasonic imaging. We have collected preliminary low-rate (0.25 to 1 Hz) indentation data on *ex-vivo* porcine liver, using the Enduratec linear actuator, 3D ultrasound system (Philips SONOS 7500, Philips Medical Systems, Andover, MA), and our perfusion apparatus. The ultrasound probe is placed under the organ, while the indenter contacts the organ on the top surface (see Figure 3), and is used to capture a 5-second volumetric response of the organ at a rate of 25 frames per second. Understanding the internal volumetric strain-field of tissue under indentation provides a distinctive "finger-print" of the organ behavior and allows us to uniquely identify its material parameters. The estimation of the organ's internal strain field is derived from the optical flow algorithm of Horn and Schunck [Horn & Schunck, 1981].

Our preliminary strain-imaging work suggested that deformation fields obtained from traditional optical flow techniques suffer from prohibitively high levels of noise present in ultrasound images. To address this we have developed a non-rigid motion tracking technique suitable for noisy datasets, which combines local optical flow measurements with a deforming finite-element model. This technique will be presented at the International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity in Texas this October [Jordan et al., 2005].

Refinement of FEM of whole organ measurements

In year 3, we found that existing models in the finite element modeling packages were unsuited to reproduce the responses that we measured from our whole organ *in vivo* and *ex vivo* tests. As a result, we began the integration of a more advanced model into the FE meshes that we had developed. This has progressed through year four to yield a suitable model and a useful parameter extraction method. The progress of year four is detailed as follows.

The large indentation creep and small strain frequency indentation studies performed to determine the effects of perfusion on the mechanical properties of the liver provided insight as how to best model the whole organ. Empirical models fit to the data support other researchers observations that the tissue has a viscoelastic response. However, we also discovered that a two time constant model is required to characterize the large deformations typical of surgical manipulations. We have hypothesized that the two time constants are from the redistribution of fluid through the liver from two distinct pathways: flow through the vasculature and flow from cellular deformation. Thus a physically based poroviscous hyperelastic constitutive model has been selected for identifying the mechanical properties of liver.

The model has been developed in collaboration with a soft tissue-modeling expert at MIT. The model has been used to successfully describe the behavior of collagen and cervical tissue [Febvay, 2003]. Using indentation data we had previously collected on breast tissue, we have studied the model and assessed its ability to model more cellular and vascular tissues. The model has three networks in parallel (see Figure 4) to describe the collective contributions of the tissues main constituents: collagen and elastin (hyperelastic network that captures the initial

elastic response), parenchyma and ground substance (viscoelastic network to capture the time dependant cellular and extracellular deformation response) and the perfusate (poroviscous network to capture the time dependant response of flow through the vasculature). A simplified version of the model was used on the breast indentation data to work through our parameter identification process and to assess the ability of this model to capture the nonlinear poroviscoelastic response of soft tissue [Kerdok, et al, 2005b].

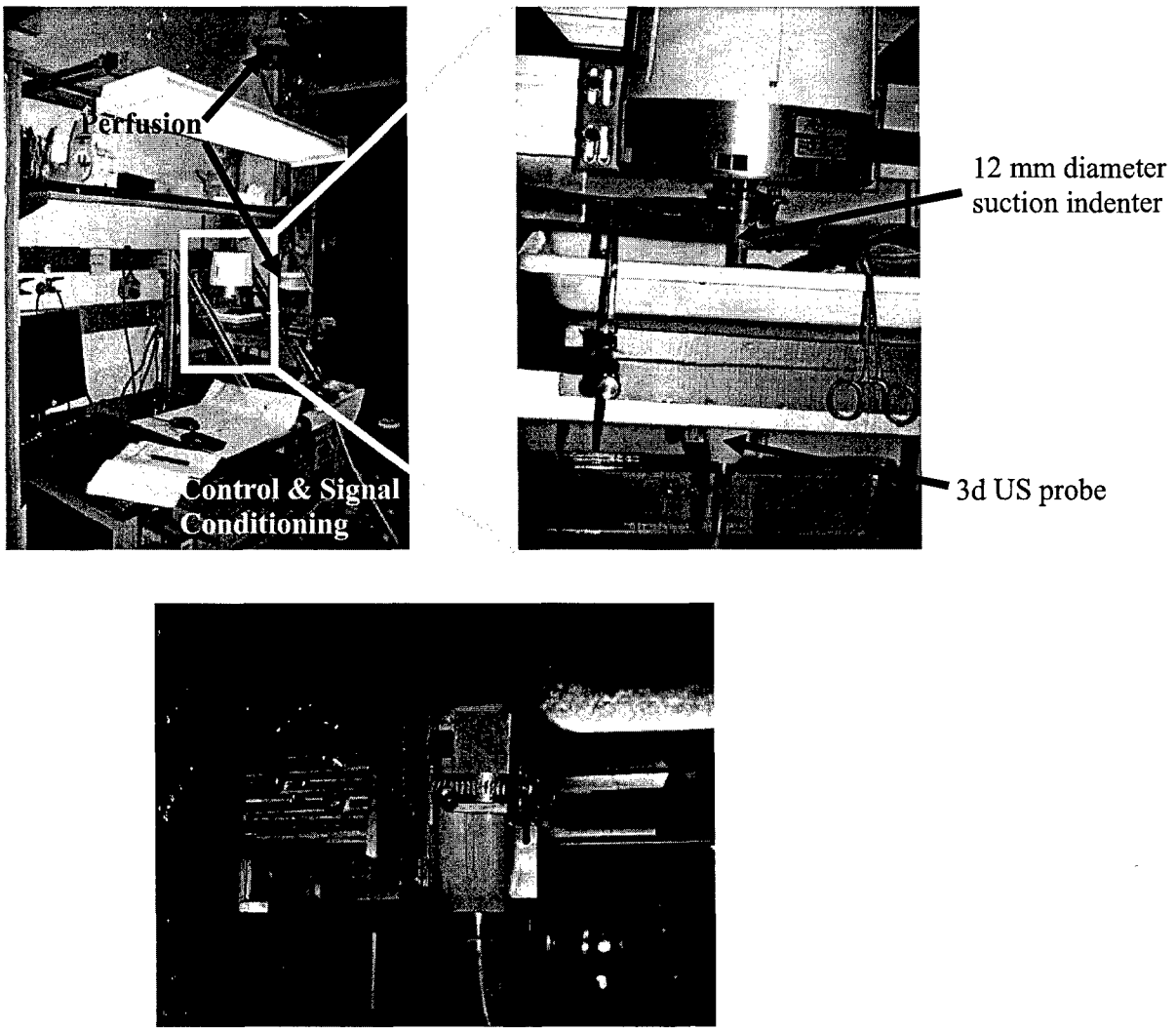

Figure 3: (A) Set-up for ex vivo perfused indentation experiments with 3d US data collection. (B) Porcine liver being loaded and imaged simultaneously in vitro. (C) Close-up of new platform set-up for large strain creep measurements with 3-D US probe.

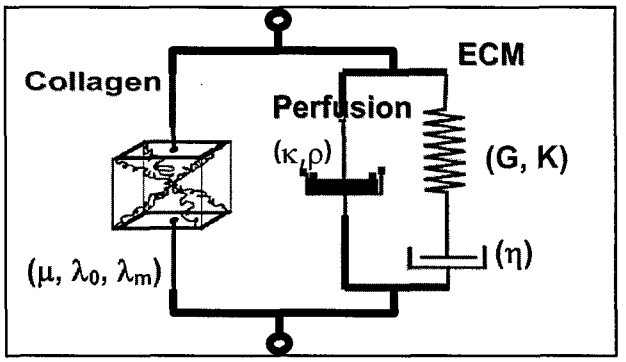

Figure 4: Rheological representation of the physically based three-network hyperelastic/poroviscous/ viscoelastic constitutive model selected for modeling the liver.

6-dof robotic measurement of renal forces / torques *in situ* for boundary effects

Robotic testing deferred

Measurements on renal tissue anticipated four years ago have been deferred as a result of the successful progress we have made studying the other tissues of interest. The use of a fully position/orientation controlled robot arm to manipulate tissues *in situ* is no longer relevant to the course that this research program has followed. However the concept will be retained for future consideration.

Optimization of FEM methods for real-time interactivity

Refined to optimization of full model for parameter identification and adaptation to real-time implementation

Among the most significant accomplishments this year was the development of techniques to extract material parameters for tissues from the experimental data. This step precedes the implementation of a useful real-time model, and provides the data to form a basis for comparison between real-time and offline model results.

We identify the material parameters of the three-network model by solving the inverse problem using large strain indentation data on soft tissues (see Figure 5). A finite element model is developed that replicates the loading and boundary conditions of the indentation experiments.

The material is defined using the constitutive law with initial values given for the model parameters. An iterative process updates these parameter values using an optimization scheme that minimizes the mean squared error between the model's response and the force vs. nominal strain data. We first tested this process using a reduced poroviscous hyperelastic model with data previously collected on breast tissue and identified a solution in its five-dimensional parameter space. We recently developed a new testing system that allows us to conduct the indentation experiments on perfused livers necessary to identify the parameters of the full model using a similar iterative optimization process (Enduratec and 3-D ultrasound system described above).

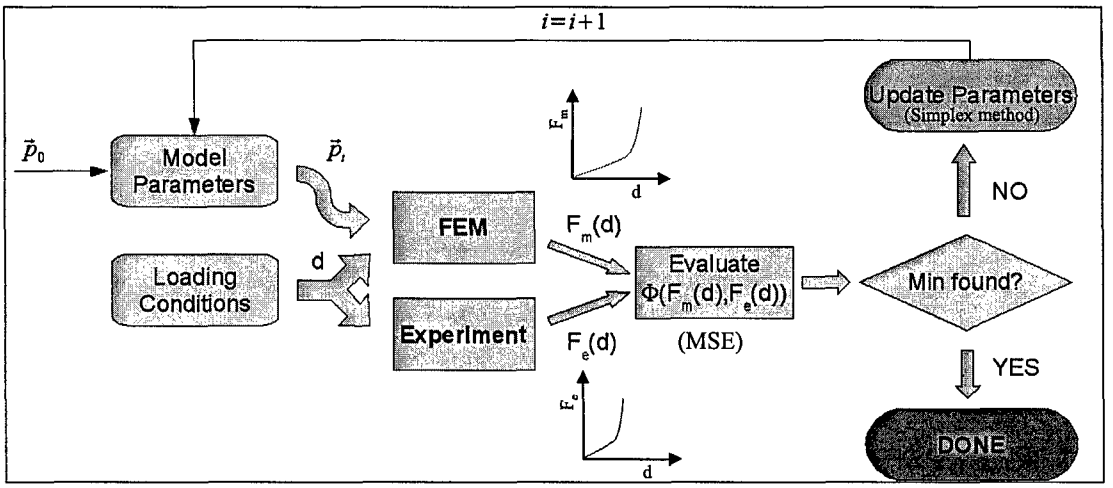

Figure 5: Iterative FEM process used to solve the inverse problem. Constitutive model parameters are identified by minimizing the mean-square error (MSE) between experimental and modeled force-displacement relationship.

Load and unload indentation tests were conducted on various *ex vivo* pathologic breast tissues using a manually driven indenter [Wellman, 1999]. An axisymmetric 2D finite-element model of the indentation tests was developed using ABAQUS 6.5-1 (HKS, Providence, RI) using hybrid quadratic triangular elements (CAX6H) (see Figure 6). A user subroutine was used to assign the constitutive model to the material and initial values for the parameters that showed reasonable agreement to the experimental data were selected. We have developed a link between Matlab (Mathworks, Natick, MA) and ABAQUS environments in order to perform the optimization, minimizing the mean-square error between the experimental and modeled force-displacement curves. The Nelder-Mead downhill simplex method was used to iteratively adjust the parameters of the model until a satisfactory match between the experiment and its model was found. Results of the optimization technique showed excellent agreement to the data suggesting that a porous hyperelastic model can adequately describe the behavior of breast tissue (see Figure 7).

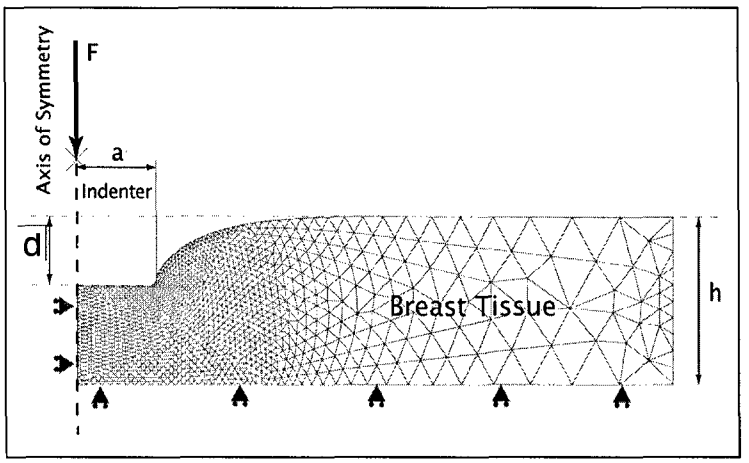

Figure 6: Finite element model of large strain indentation of soft tissue.

One lesson learned from using the breast data to work through the parameter identification process is that manually collected data is too noisy and inconsistent to obtain a

unique and optimal model fit. Similarly, the *ex vivo* boundary conditions were not completely frictionless, the samples were very thin, and more displacement histories than load/unload will be necessary to uniquely identify the material parameters of soft tissue. The Enduratec instrument was developed to address these issues.

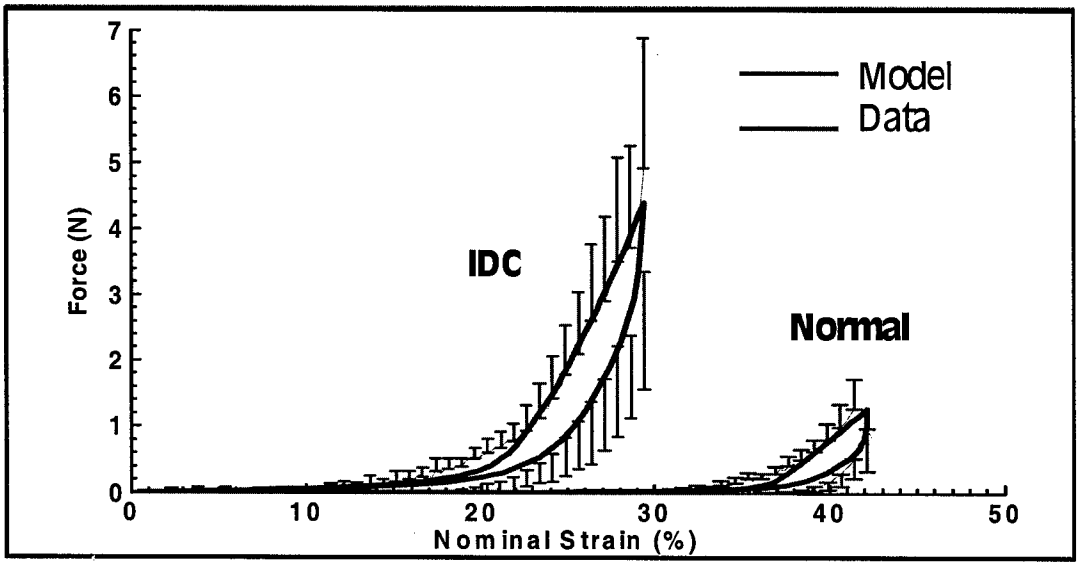

Figure 7: Example of pathologic and normal breast tissue indentation data +/- standard deviation, and optimized model fit.

We have been working on implementing the model in real-time using uniaxial compression breast data and a modified version of the model written to run in Matlab. We anticipate results in this effort in the upcoming extension period of this contract.

Possible human tissue measurements of tissue pre-resection (indentation and implanted devices)

Protocols to be developed during extension period

As described earlier, we have performed analysis on data that were obtained from human breast tissue samples in earlier work performed by the Biorobotics Laboratory, leading to the development of our modeling techniques. As a result of the lessons learned and developments of new instrumentation for *ex vivo* testing, we have not reached the point of performing tests on human tissues to date. Having successfully developed our testing protocols, we will endeavor to adapt them to the rigors and restrictions regarding the handling of human tissues, and prepare an experimental protocol for such testing during the extension period of this contract.

Given the harsh conditions imposed by mechanical testing on soft tissues, a new method for collecting human data is under consideration. Occlusion balloon catheters are used to measure hepatic pressures via the hepatic veins. An initial investigation of the anatomy suggests that the hepatic veins are unique in that there is little to no vascular content to them, simply a 1cell thick endothelium lining. We believe that these balloon catheters can be modified to make pressure volume measurements of the livers parenchyma via the hepatic vein. We plan to pursue this concept and make some preliminary measurements during the extension period.

FEM modeling of possible human measurements

This topic has similarly been deferred with the exception of analysis performed on human breast tissue samples, which was described above.

External measurements and analysis of Truth Cube 2 silicone test objects

Year four saw the completion of analysis performed by collaborators at ETH Zurich on the Truth Cube 2 that we developed previously [Hollenstein, 2005]. The standard test objects that we constructed were tested first with the TeMPeST 1-D device, measured with a standard rheological tester (courtesy of colleagues at the MIT Institute for Soldier Nanotechnologies) and indented using a series of fixed loads with a spherical indentation probe while being scanned with a CT imager to generate internal deformation field information. The objects were then transferred to ETH Zurich for further testing with an aspiration (suction) probe, a torsional resonator device and a standard materials testing system to perform uniaxial compression.

Hollenstein investigated the modeling of the deformations imposed under all of these conditions and calculated the material parameters of the Truth Cube silicone for each (see Figure 8), showing good agreement between the quasi-static tests (aspiration and compression), and similar trends between the TeMPeST and the rheological testing, though in these measurements the magnitude of the measured elasticity differed by 40%. The measurements made using the torsional resonator device extend from frequencies one to two orders of magnitude higher than either the TeMPeST or the rheological tester, and extrapolation to those devices' results is not determinative. However, Hollenstein suggests that the lower values measured by the rheological tester and other techniques are more likely to be accurate in magnitude than those made with the TeMPeST in this case.

A conference paper has been submitted to the International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity based on this work, and we will be preparing a journal article fully describing the experiments during the extension period.

High rate abdominal tissue testing devices and low rate brain testing device development

We have continued our involvement with the behind-armor tissue modeling and measurement work being done at the MIT Institute for Soldier Nanotechnologies, as the devices under development will contribute to our ability to measure the organs and tissues of interest under this research program.

At present, a prototype device for low to medium depth impact testing has been constructed and is serving as a model for second device that will be useable in either the *ex vivo* or *in vivo* environments (see Figure 9). A larger deformation version of a TeMPeST-like device is also under construction, enabling larger deformations similar to those that we have made with the Enduratec system, but aimed for use in the *in vivo* environment. In addition to these higher rate dynamic devices, development is continuing on a quasi-static probe that will be used to evaluate brain tissue properties *in vivo* on porcine models.

Experimental protocols to support the planned animal testing have been prepared and approved by the relevant institutions. No funding from this contract will be used to support the performance of these animal tests.

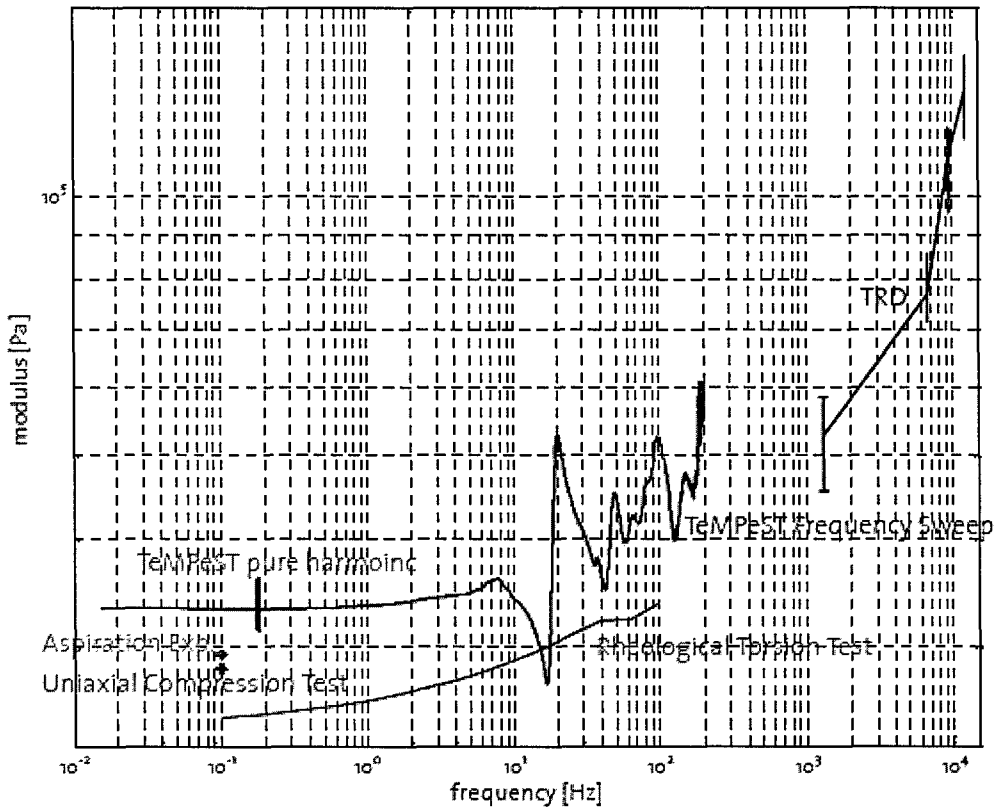

Figure 8: Young's Modulus vs. Frequency: different methods of soft material characterization provide a complete picture of the silicone mechanical properties (source: Hollenstein, 2005).

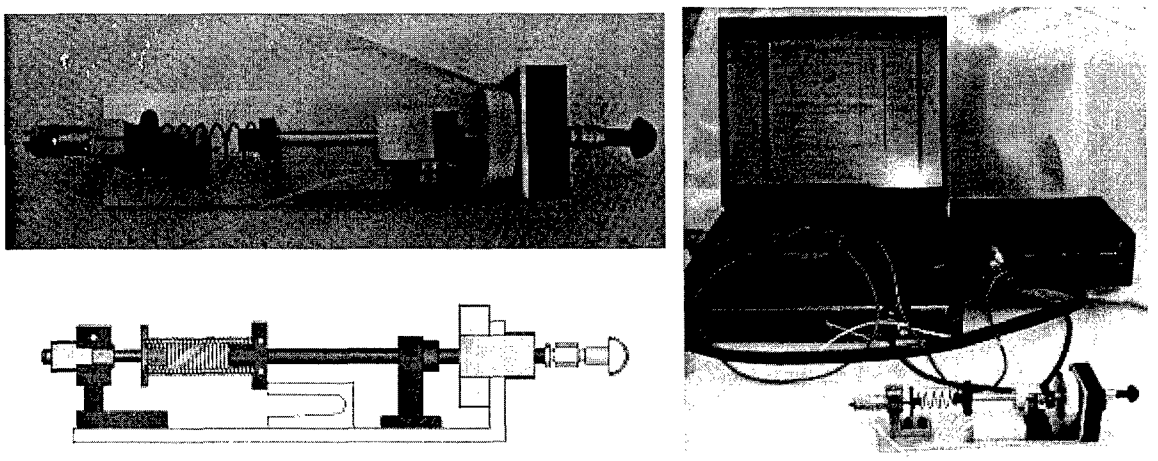

Figure 9: Abdominal tissue high speed impact testing instrument prototype.

Completion of miniature force sensor for vocal tissue testing

The vocal tissue testing instrument described in last year's report continues to approach completion. The most significant milestone reached in this year was the construction of a miniature force sensor suitable for use under laryngoscopic access to the tissues. It has been

mounted to the instrument developed during year three, and is currently undergoing testing and refinement.

Key Research Accomplishments

- Completed development of a useful and detailed model for describing the poroviscous-hyperelastic character of the tissues of interest
- Developed inverse techniques for the extraction of the characteristic parameters from this model, using existing pathological breast tissue data as a data source
- Constructed new large strain, moderate rate, high fidelity bench-top indentation system to greatly improve on the variety of testing that can be performed beyond the manual large deformation indenter of years 2 and 3
- Combined new indentation system with 3-D ultrasound scanning apparatus to simultaneously apply known loads and deformations and determine the internal deformations to improve the uniqueness of the parameters extracted from the model
- Collected data from 5 perfused porcine livers using new indentation system, 3 with combined indentation/3-D ultrasound apparatus
- Developed new algorithms to measure the internal strain field from data with low signal to noise ratios.
- Analysis of the truth cube results that we obtained and significant further measurement and comparison between measurement techniques by our international collaborators;
- Guided construction of prototypes of *in vivo* high speed testing devices developed in with MIT which will be used for abdominal organ tissues and design of an instrument for the measurement of porcine brain tissues
- Constructed miniature force sensor for used on laryngoscopic vocal tissue testing device.

Reportable Outcomes

Journal papers

- [1]Kerdok, A.E., Ottensmeyer, M.P., Howe, R.D., The Effects of Perfusion on the Viscoelastic Characteristics of Liver, *Journal of Biomechanics*, in press, 2005.

Conference papers

- Kerdok, A.E., Howe, R.D., Characterizing large deformation behavior of liver for surgical simulation. In Proceedings of Biomedical Engineering Society Annual Meeting. Baltimore, MD, 2005 **(poster presentation).**

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[1] Paper preprint included in Appendix A

- Jordan, P., Kerdok, A.E., Socrate, S., Howe, R.D., Breast tissue parameter identification for a nonlinear constitutive model. In Proceedings of Biomedical Engineering Society Annual Meeting. Baltimore, MD, 2005 **(poster presentation).**
- [2]Kerdok, A.E., Jordan, P., Liu, Y., Wellman, P.S., Socrate, S., Howe, R.D., Identification of nonlinear constitutive law parameters of breast tissue. In Proceedings of ASME Summer Bioengineering Conference. Vail, CO, June 22-26, 2005. **(poster presentation)**
- Kerdok, A.E.,Howe, R.D., A physical basis for a two time constant constitutive model for liver. In Proceedings of ASME Summer Bioengineering Conference. Vail, CO, June 22-26, 2005. **(poster presentation, won Honorable mention for PhD Student Poster competition)**
- [2]Jordan, P., Zickler, T., Socrate, S., Howe, R.D., "Non-Rigid Soft Tissue Tracking with Three-Dimensional Ultrasound." 4th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity. Austin, TX, 2005. **(poster presentation)**
- Kerdok, A. E., Socrate, S. & Howe, R. D. 2004. "Soft Tissue Modeling and Mechanics". In American Society of Biomechanics Annual Meeting 2004 (ed. M. Bottlang & S. M. Madey). Portland, OR. **(poster presentation)**

Contributed Conference Papers and Presentations

- Kerdok, A.E., Howe, R.D., Dawson, S.L., Socrate, S., Mechanical characterization of liver for surgical simulation. Presented at Industrial Outreach Program. Harvard University, 2005. **(poster presentation)**
- Kerdok, A. E., Howe, R.D. "Characterizing Large Deformation Behavior of Liver for Surgical Simulation," HST Forum, Boston, MA. **(poster presentation)**
- Jordan, P., Howe, R.D. "Identifying the Parameters of a Nonlinear Constitutive Law for Soft Tissue Using Three-Dimensional Ultrasound Imaging." HST Forum, Boston, MA. **(poster presentation)**

Conclusions

As was done in year three, significant progress was made towards our goal of developing advanced techniques to determine the behavior of soft biological tissues. The learning experiences of the previous years have led to the collection of new data and extraction of useful tissue property parameters, and have guided the research in interesting new, and sometimes unexpected directions.

With respect to instrumentation, a new motorized large deformation indenter has superseded the manual device developed previously, and is allowing us to generate high quality data repeatably, and perform a wider variety of tests than the step and hold available previously. Further, it has been integrated with the 3-D ultrasound scanning system to allow us to measure not only the force and depth of indentation, but also the internal deformation field of the tissue.

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[2] Abstract included in Appendix A

These data will be fit to the poroviscous hyperelastic model that we have developed and through techniques that have been developed this year, will allow us to extract the numerical parameters that characterize the tissues. The model itself is a major step forward, as it encompasses all of the responses that we have observed in testing the tissues, and will therefore serve as a standard from which we will be developing our real-time implementations for performing soft tissue simulation. The real-time implementation will, of necessity, be a reduced version of the full model, but will be directly comparable to results determined from the full version. The model and the optimization techniques for parameter determination are directly applicable to the other tissue types that we will be studying during the extension period of this grant.

Our collaborative efforts, which stemmed from our early successes in performing this research continue to be fruitful.

The additional work that we performed in developing and testing the Truth Cube and Truth Cube 2 has lead colleagues at ETH Zurich to extend the measurements and perform detailed comparisons of a variety of testing techniques, highlighting the capabilities and shortcomings of each. The results show that our techniques do align with each other, and contribute data to help describe the materials over a wide range of frequencies.

The MIT and MGH collaborations have resulted in the development of instrumentation to explore different ranges of responses of our chosen tissues, as well as devices to examine tissues of interest beyond them. Prototypes of a solid organ impact tester, a vocal tissue testing instrument, an *in vivo* large deformation indenter and a quasi-static brain tissue tester have all been generated during this past year. Results will begin to be obtained during the extension period, and into research efforts that will extend beyond that.

Certain departures have been made from the original Statement of Work, based on our research findings, and this is an expected development. Developing the test apparatus and protocols for the most difficult organ (liver), has lead to the delay in testing other animal tissues (spleen and kidney), and as a result, human tissue testing (which was considered as a possibility early on) has also been delayed. We have requested a no cost extension to this grant which will allow us to pursue these goals. We also originally expected to perform tests on the gross motion of whole organs by using an industrial robotic system to manipulate the kidney in six degrees of freedom. Our work in developing systems to preserve the internal boundary conditions of organs (the perfusion system) has been at least as valuable in acquiring accurate tissue data as the robotic manipulation of tissues *in situ* (but *post mortem*) would have been. This work may be pursued in research extending beyond the completion of this grant.

So What?

In examining the value of the research completed to date as a scientific or medical product, we consider the broader importance of the work, its utility to researchers and developers beyond our own group, and the contribution to the body of biomechanics knowledge and the collection of techniques for generating this information.

A primary goal of medical simulation is the improvement of patient safety. This is accomplished by providing realistic training tools so that medical practitioners may hone their skills significantly before performing interventions on real patients. Until recently, the only realistic tools available in many cases were animal models, which have limitations in realism, financial cost and the numbers of animals that can ethically be used for training. Realistic training tools "*in silico*" rely on a body of information including the mathematical

characterization of living tissues, and can improve the realism over the animal models and allow for unlimited rehearsal on a potentially very wide range of anatomies and pathologies.

Our work continues to add to the body of data describing the characteristics of living tissues by creating mathematical models and determining the parameters describing each type of tissue. We have done this by creating and improving upon a suite of instruments purpose built to measure tissues initially *in vivo* and now *ex vivo* yet with elements that maintain tissues in a near *in vivo* state. This too minimizes the number of animals required to populate an atlas of tissue models and properties.

The development of the perfusion system and its publication in this year provides other researchers with a system that can be implemented in their laboratories to enable improved quality measurements for their tissue testing experiments. Similarly, the instrumentation that we've developed under this grant has enough general utility that it will likely continue to be used in the future to measure the mechanical properties of other tissues and soft non-biological materials.

The mathematical models have been implemented in our own finite element analysis code, and can be ported to other researchers' systems so that if they have a need to simulate the behavior of tissues, they can rely on an accurate physics-based model whose parameters were determined from measurements on real tissues. This will have applications for surgical planning and medical instrument design, as the interactions between CAD models of instruments and mathematical models of tissues will be possible to simulate. Efforts are underway to generate real-time implementations of the model that will be useful in interactive medical simulators, specifically aimed at medical training.

With respect to human tissues, experimental protocols and additional instruments that would be suitable for *ex vivo* and later on, *in vivo* testing are under development. These data will ultimately be the ones most desired for medical simulation, and we will also be able to quantify how the same tissues in different organisms behave differently (e.g. is porcine liver biomechanically very similar to or different from human liver).

Thus, the research project that we embarked upon four years ago has had benefits not only in terms of academic achievements such as publications, but also towards the development of tools that are useful in the research arena, will be useful in the areas of medical device and procedure development, and will have benefits for patient safety through improved training methods for the practitioners of medicine.

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Appendix A: Papers, Abstracts, Supporting Material

- Kerdok, A.E., Ottensmeyer, M.P., Howe, R.D., The Effects of Perfusion on the Viscoelastic Characteristics of Liver, *Journal of Biomechanics*, in press, 2005.
- Jordan, P., Zickler, T., Socrate, S., Howe, R.D., "Non-Rigid Soft Tissue Tracking with Three-Dimensional Ultrasound." 4th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity. Austin, TX, 2005. **(poster presentation)**
- Kerdok, A.E., Jordan, P., Liu, Y., Wellman, P.S., Socrate, S., Howe, R.D., Identification of nonlinear constitutive law parameters of breast tissue. In Proceedings of ASME Summer Bioengineering Conference. Vail, CO, June 22-26, 2005.

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Effects of perfusion on the viscoelastic characteristics of liver

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Abstract

Accurate characterization of soft tissue material properties is required to enable new computer-aided medical technologies such as surgical training and planning. The current means of acquiring these properties in the in vivo and ex vivo states is fraught with problems, including limited accessibility and unknown boundary conditions in the former, and unnatural behavior in the latter. This paper presents a new testing method where a whole porcine liver is perfused under physiologic conditions and tested in an ex vivo setting. To characterize the effects of perfusion on the viscoelastic response of liver, indentation devices made force and displacement measurements across four conditions: in vivo, ex vivo perfused, ex vivo post perfused, and in vitro on an excised section. One device imposed cyclic perturbations on the liver's surface, inducing nominal strains up to 5% at frequencies from 0.1 to 200 Hz. The other device measured 300 s of the organ's creep response to applied loads, inducing nominal surface stresses of 6.9–34.7 kPa and nominal strains up to 50%. Results from empirical models indicate that the viscoelastic properties of liver change with perfusion and that two time constants on the order of 1.86 and 51.3 s can characterize the liver under large strains typical of surgical manipulation across time periods up to 300 s. Unperfused conditions were stiffer and more viscous than the in vivo state, resulting in permanent strain deformation with repeated indentations. Conversely, the responses from the ex vivo perfusion condition closely approximated the in vivo response.

Keywords: Perfusion; Viscoelastic; Indentation; Creep; Liver; Large strain

1. Introduction

The development of minimally invasive surgical procedures has induced a need for new surgical training and planning methods. Computer simulations of these procedures provide a platform for such training, yet their utility is currently limited by a lack of data on the realistic behavior of soft tissues under deformations typical of surgical manipulations (Delingette, 1998; Fung, 1993; Szekely et al., 2000). Characterizing the heterogeneous, nonlinear viscoelastic behavior of soft nonload-bearing tissues is a difficult challenge. A standard method for testing soft tissues is needed to produce repeatable results that can be mathematically modeled to capture the natural behavior of the tissue.

Realistic tissue characterization via constitutive modeling requires concurrent control of both geometric and physiologic boundary conditions. Typically, force–displacement responses of soft tissues are collected under two conditions: in vivo and ex vivo. In vivo testing maintains the natural state of the tissue, but there are accessibility issues, ill-defined boundary conditions, and ethical issues related to the use of animals and potential risk to human subjects. Researchers have made in vivo mechanical measurements, but the limited data sets, small deformations atypical of surgical manipulations, difficulty in obtaining proper instrument alignment on sizable specimens, complications from physiological noise, and the inability to account for and control the

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internal condition of the organ make interpreting the data difficult (Brouwer et al., 2001; Brown et al., 2002, 2003; Carter et al., 2001; Gefen and Margulies, 2004; Kalanovic et al., 2003; Kauer et al., 2001; Kim et al., 2003; Melvin et al., 1973; Ottensmeyer, 2002; Ottensmeyer and Salisbury, 2001; Rosen et al., 1999; Tay et al., 2002). Ex vivo experiments are good for device, protocol, and model development, as well as for ease of testing, ethical considerations, and boundary condition control. Many attempts have been made to measure the material properties of soft nonload-bearing tissues ex vivo (Dokos et al., 2000; Hu and Desai, 2004; Liu and Bilston, 2002; Miller, 2001; Miller et al., 2000; Nava et al., 2003; Valtorta and Mazza, 2004) despite knowledge that the mechanical properties are altered post mortem (Fung, 1993; Platz et al., 1997; Schon et al., 2001; Yamada, 1970).

These considerations show the importance of understanding the differences in the tissue's mechanical response between the in vivo and ex vivo conditions (Brown et al., 2003; Gefen and Margulies, 2004), and the need for developing a new testing method that incorporates the strengths of both. In this study, we introduce an ex vivo perfusion system that permits carefully controlled mechanical measurements on porcine liver in a nearly in vivo state. Although no ex vivo setup will completely replicate the organ's natural in vivo condition, we hypothesize that maintaining temperature, surface hydration, and vascular pressure to physiologic levels using a physiologic perfusate can closely approximate it. Two indentation devices were used to assess the mechanical properties on freshly harvested whole porcine livers using the perfusion system. One measures small strains across a range of frequencies and the other measures large-strain creep responses over time. Tests at the same locations on the same livers allowed comparisons of the results across four different conditions: in vivo, ex vivo perfused, ex vivo post perfused, and in vitro on an excised section. Fitting the data to empirical models provided a quantitative comparison and time scale estimation of the viscoelastic response of liver across conditions. In addition, a histological comparison is made from biopsies taken during testing.

2. Methods and materials

2.1. Ex vivo liver perfusion system

The liver is a highly vascular organ perfused with 0.5–1 l of blood (Crawford et al., 1998). It contains two inlets on the inferior side: a low-pressure portal vein accounting for 75% of the volume and a high-pressure hepatic artery accounting for the remaining 25%. The low-pressure hepatic vein serves as the outlet on the superior side, draining into the inferior vena cava.

We have built a system that attempts to maintain the mechanical integrity of a whole liver while mimicking physiologic conditions in an ex vivo setting. The perfusion system (Fig. 1) maintains temperature, surface hydration, and pressure for a whole porcine liver ex vivo. Veterinary lactated Ringer's solution (Henry Schein, Melville, NY) hydrostatically maintains physiologic pressures of 97 ± 5 mmHg to the hepatic artery and 18 ± 2 mmHg to the portal vein. The perfusate is allowed to drain via the intrahepatic vena cava into a bath where it is heated to 39 °C (porcine core temperature) and circulated to the arterial reservoir via a pump. The arterial reservoir overflow feeds the portal venous reservoir whose overflow provides hydration to the organ's surface without submerging the organ. To ensure consistency in our measurements, the organ rests on a sturdy plate covered with fine grit sandpaper to stabilize the area of tissue under study. The perfusion pressure is held constant, rather than mimicking physiologic pulsatile pressure to enable accurate force–displacement measurements.

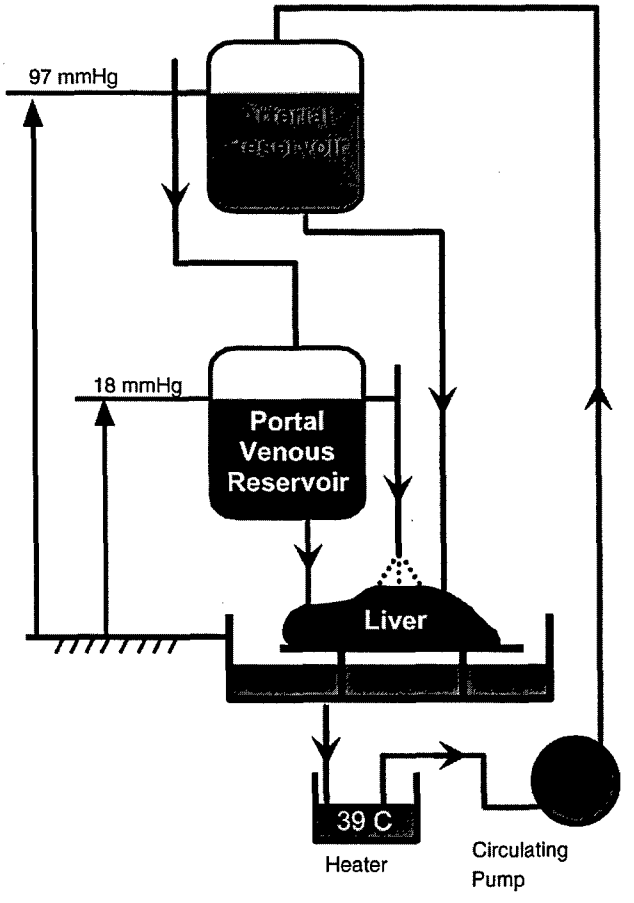

Fig. 1. The ex vivo liver perfusion system.

2.2. Indentation test instruments

Two indentation instruments were used to acquire viscoelastic mechanical measurements on the surface of intact livers across conditions. The Tissue Material Property Sampling Tool (TeMPeST) examined the small-strain (0–5%) frequency response (0.1–200 Hz) (Ottensmeyer and Salisbury, 2001), while a creep indentation device captured the large-strain (10–50%) time domain response (over 300 s).

The TeMPeST measures the small-strain compliance of solid organs (Fig. 2A). A 5 mm circular punch vibrates the tissue while recording applied load (LPM 562 force sensor, Cooper Instruments, Warrenton, VA) and relative displacement (099 XS-B LVDT position sensor, Schaevitz, Hampton, VA). A voice coil motor is controlled in open loop mode, using commanded current as a proxy for applied force. The sampling frequency of 2 kHz enables measurements to approximately 200 Hz. The range of motion is 1 mm (RMS 0.18 μm) and forces can be exerted up to 300 mN (RMS 0.15 mN) (Ottensmeyer, 2001).

For this study, the TeMPeST applied a sinusoidal indentation force with monotonically increasing or decreasing frequency (chirp) to the tissue between 0.1 and 200 Hz, under either a 45 or 90 mN nominal preload force (actual mean loads varied between 10 and 70 mN due to tissue relaxation) and a nominal amplitude of 30 mN (measured between 4 and 10 mN below instrument resonance (80 Hz), and up to 30 mN at resonance) to avoid loss of tissue contact. In these tests, only relative displacement from the preloaded depth could be measured. A minimum of five tests was done for each condition at each location with roughly 11 indentations per test. One data set was collected every 2–3 min, with the actual time of testing taking 16.4 s in vivo and 32.8 s ex vivo.

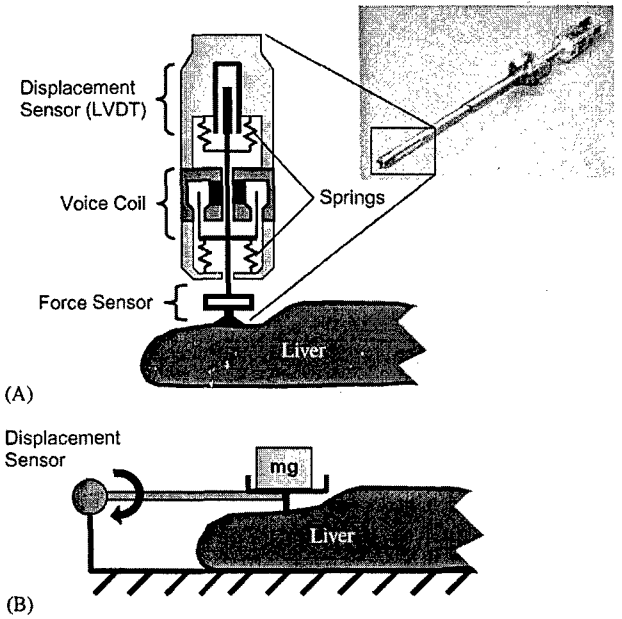

Fig. 2. (A) Small-strain frequency response device. Detail shows the voice coil driven indenter with flextures and sensors. (B) Large-strain creep indentation device.

The creep indenter performed normal indentation tests with large strains typical of surgical manipulations (Fig. 2B). The device was rigidly mounted to the same platen on which the liver rests to avoid relative motion artifacts. A 6 mm diameter flat cylindrical punch rests on the tissue surface with only 3 g load due to counterweights. A standard laboratory brass weight was placed at near-zero velocity onto a platform mounted coaxially with the indenter tip. An 11.5 cm lever arm with 4 cm of vertical travel connected the indenter to the base, allowing measurements nearly anywhere on the organ surface. Applied loads of 20 and 100 g generated nominal surface stresses of 6.9 and 34.7 kPa, respectively, which are lower than the liver's reported failure stress of 232 kPa (Melvin et al., 1973) and breaking stress 451 kPa (Seki and Iwamoto, 1998). The angular position of the measurement arm was sampled at 1 kHz using a miniature contactless rotary position sensor (Midori America Corporation, Fullerton, CA) (resolution 11 μm, RMS 20 μm) over 5 min. Organ thickness measurements were taken prior to every indentation measurement with a dial indicator for purposes of reporting nominal strain (displacement/preindented thickness).

2.3. Experimental protocol and environmental conditions

Livers from four pigs 27–37 kg (mean 32.5 kg) were used in this study. All were tested in vivo, ex vivo perfused, and ex vivo post perfused, while three had sections removed for in vitro testing. The total duration of testing varied based on number of locations and indentations, but on average, the total test time was between 5 and 8 h. The experimental protocol was approved by the Harvard Medical School Center for Animal Resources & Comparative Medicine Institutional Review Board. An additional pig was used for an independent study on the unperfused condition.

Samples for histological analysis were taken in three of the livers using a 15-gauge core biopsy needle (Meditech Boston Scientific, Watertown, MA) on a lobe of the liver that was not tested. A control sample was taken immediately post sacrifice and again post harvest after flushing with the perfusate. Samples were then taken every hour across all conditions tested, including one upon test completion (24 samples in total), stored in 10% buffered formalin for 36 h and then transferred to 70% alcohol for transport to a histology laboratory (Mass Histology Service, Warwick, RI). A grid report of the hematoxylin and eosin stains was

obtained from a pathologist to determine cellular damage and structural integrity across conditions.

2.4. In vivo whole organ testing

In vivo tests were performed on deeply anesthetized animals on assisted ventilation with 100% oxygen. The abdomen of the pig was exposed and a lobe of the liver was situated on the platen of the creep device. Locations where the thickness was between 20 and 37 mm (mean 24.8 mm) were chosen and marked with a tissue-marking pen. The TeMPeST acquired compliance data on the liver for periods of 20 s. Ventilation was suspended to prevent pulmonary motions from saturating the position sensor measurements. Indentations using the creep device were made at the same locations, but without the necessity for suspending ventilation. Two to four indentations using both the 20 and 100 g loads were made at each location. Initial position sensor values were noted and the load was applied in pseudo-random order for 300 s, with repetition of the first load at the end. The organ was allowed to recover to within 1 mm of its preindented state (typically 200 s) before applying the next load. The total time for in vivo testing was between 1.5 and 3 h, depending on the number of tests performed.

2.5. In vitro excised section testing

Following in vivo testing, heparin was injected systemically to minimize clotting (1 ml/10 kg of 1000 units/ml) and the animal was sacrificed with an injection of KCl. The liver was harvested, and a lobe was removed and tested immediately with the TeMPeST (in vitro excised section testing). The cut surface of the remainder of the organ was cauterized to prevent leakage and the organ was flushed with 1 l of heparinized (5000 units) cold lactated Ringer's solution. The samples were packed on ice and transported to the laboratory. The excised section was tested again with the TeMPeST in the same locations at room temperature approximately every 20 min. This condition most closely represents many previous ex vivo tests: blood-filled cut sections tested at room temperature several hours post mortem (Dokos et al., 2000; Hu and Desai, 2004; Liu and Bilston, 2002; Miller, 2001; Miller et al., 2000; Nava et al., 2003; Valtorta and Mazza, 2004). Long data collection periods for the creep device precluded timely collection of both ex vivo perfused and in vitro excised measurements. The number of in vitro indentations was therefore limited in favor of gathering more complete ex vivo perfused data. One of the excised lobes was tested with both instruments post mortem and again at the laboratory using the 20 g load for the creep device.

2.6. Ex vivo perfused whole organ testing

Upon arrival at the laboratory (114 ± 22 min of cold ischemic time post mortem), the hepatic artery and portal veins of the liver were sutured to the arterial and portal venous perfusate reservoir tubing. Perfusion was begun and the organ was allowed to come to physiological temperature before testing was resumed within 20 min. A cannula was sutured to the hepatic inferior vena cava to keep the outflow patent. TeMPeST and creep indentation tests were performed in the same manner and at the same locations as the in vivo tests to adequately compare across conditions and minimize variation in the measurements due to unknown locations of large vessels or connective tissues within the organ. The total time for ex vivo perfused testing was 183 ± 47 min depending on the number of locations tested.

2.7. Ex vivo post-perfused whole organ testing

Following the completion of testing on the perfused organ, the inlet tubes were clamped to stop the flow, while the outlet remained patent. The organ was tested again with both instruments in the same locations to observe any further changes in the response, typically 30–60 min. The creep device applied 3–4 sequential indentations, one every 10–20 min. Since initial trials had revealed that the tissue's response changed with indentation in the unperfused states and because we were interested in the large-strain response, only the 100 g load was used.

2.8. Ex vivo whole organ independent post-perfused test over time

To ensure that the differences in the responses seen between the ex vivo whole organ perfused test and the ex vivo whole organ post-perfused test was not due to the latter occurring after the perfusion test, we conducted an independent ex vivo post-perfused test. A 30 kg pig was systemically heparinized and sacrificed, and the liver was harvested and flushed as described above. The liver was brought to the laboratory on ice, flushed again with perfusate at 39 °C, and the inlets were clamped as in the post-perfused condition. Creep measurements using 100 g were made on the same location (22.8 mm thick) beginning 100 min post sacrifice. Measurements were taken every 20 min for 100 min.

2.9. Data analysis—lumped element modeling

To compare the effects of environmental conditions on the viscoelastic properties of porcine livers, the data were fit to empirical first-order (TeMPeST) and second-order (creep device) lumped element models (Fig. 3).

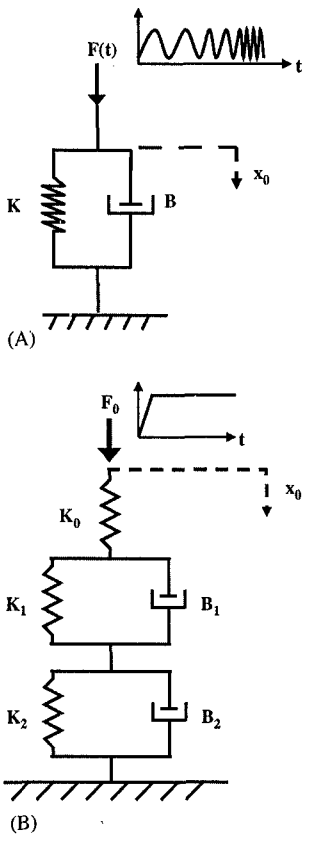

Fig. 3. Lumped element models used to quantitatively describe the tissue response. (A) First-order Voigt model for small-strain response to a force input of a sinusoidal frequency chirp $F(t)$. (B) Second-order model for large-strain response to a step load F_0.

These models are not material constitutive laws, but rather a means of quantifying the differences seen across conditions and to determine the time scales of the tissue's viscoelasticity.

The simplest model that captures small-deformation viscoelastic behavior is the first-order parallel spring-dashpot (Voigt) model (Fig. 3A). Fitting this model to the TeMPeST data involved calculating the frequency-dependent complex compliance of the tissue by taking the ratio of the fast Fourier transforms of the position and force signals over the frequency range of interest. A characteristic Voigt model curve was fit to each of the unfiltered compliance versus frequency data sets by minimizing the sum of squared errors. This yielded the static compliance (inverse stiffness $1/K$, m/N) and the characteristic (break) frequency (f_c, Hz). The damping constant of the Voigt model was then calculated as $B = K/(2\pi f_c)$.

A first-order model showed poor agreement for the creep results and a second-order model was used (Fig. 3B). The position and time data from the creep indentation device were filtered forward and backward using a second-order low-pass Butterworth filter with a cutoff frequency of 50 Hz. Since instantaneous load application is not possible, the creep tests were divided into loading (ramp) and response phases. An independent test measured the time of load application using a force sensor: the duration of the ramp phase was $t = 0-0.163$ and 0–0.236 s for the 20 and 100 g loads, respectively. The response

$$x_0(t) = A_0 - A_1 e^{-t/\tau_1} - A_2 e^{-t/\tau_2}$$

was fit from the end of the ramp phase to 290 s, where A_0 is the amplitude of the steady-state displacement defined by $A_0 = F_0(1/K_0 + 1/K_1 + 1/K_2)$, and $A_1 = F_0/K_1$ and $A_2 = F_0/K_2$ are the amplitude contributions from the creep time constants $\tau_1 = B_1/K_1$ and $\tau_2 = B_2/K_2$. A gradient decent search was performed to minimize the normalized mean square error (MSE) between the model response and data.

3. Results

3.1. Frequency response indentation tests

Typical compliance and phase versus frequency plots with the model fit for the ex vivo perfused condition under a low preload (mean = 24.7 mN) are shown in Fig. 4. The first-order Voigt model captures the nearly in-phase variation between force and displacement at low frequencies and the 90° phase shift at the upper end

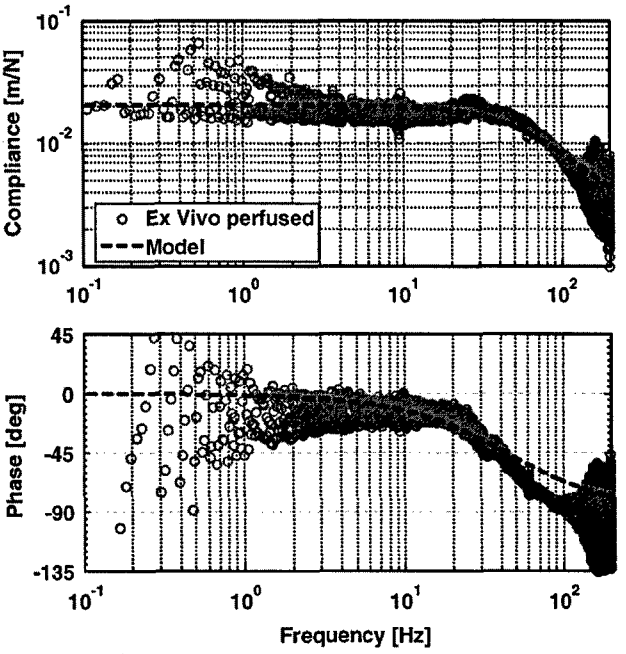

Fig. 4. Typical Bode plot of compliance (top) and phase (bottom) versus frequency. The circles are data from an ex vivo perfused test under a low preload (24.7 mN) and the dashed line is the Voigt model fit.

of the measured frequency range. Below ~40 Hz the tissue behaves like a linear elastic spring with compliance ~0.02 m/N, while above 40 Hz the viscous behavior is evident. The observed low-frequency noise is a result of the tissue's inherent nonlinearity; the nonlinear stiffness results in a distorted sinusoidal response, leading to oscillations in the Fourier transform of the measured position and force signals. This oscillation is greatly reduced when testing linearly elastic materials.

The mean and standard deviation of compliance and damping constant versus mean preloaded force for all conditions are shown in Fig. 5. The variation in preload force is due to stress relaxation. These results illustrate that both tissue stiffness (1/compliance) and damping coefficient increase with applied load in all cases.

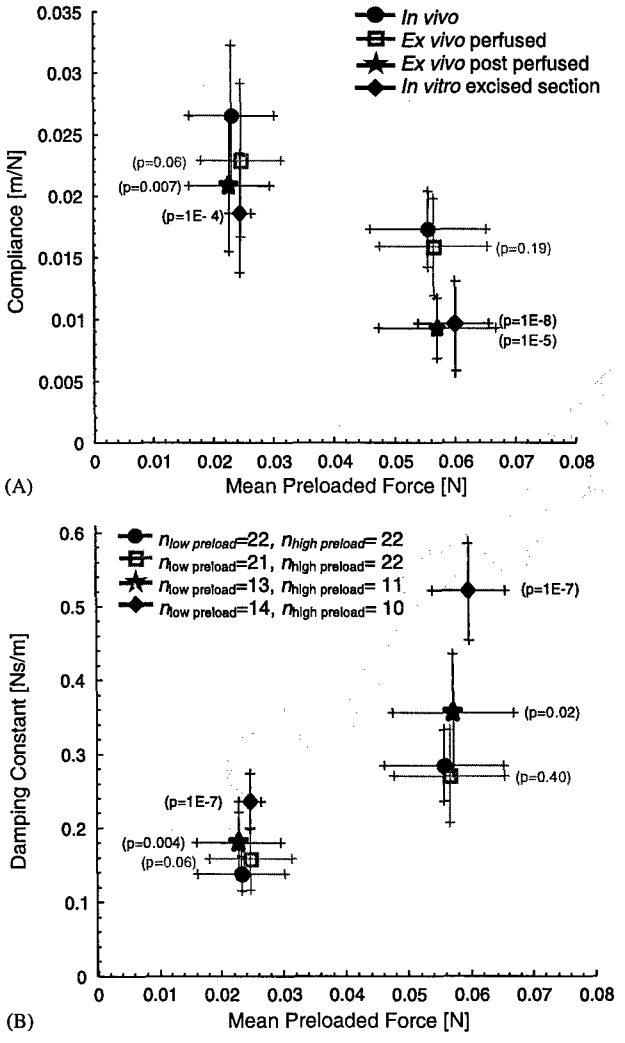

Fig. 5. Model parameters from the small-strain frequency response. (A) Mean compliance versus preloaded force ± standard deviation (SD) and (B) mean damping constant versus preloaded force ± SD for each condition. p-values for all cases compared to the in vivo case are shown next to their corresponding mean values.

A two-sample, two-tailed Student's t-test assuming unequal variances was conducted on the means of both parameters for each preload and compared to the in vivo condition with a 5% significance level. The compliance and damping coefficient for the ex vivo perfused condition were statistically the same as those for the in vivo condition under the same preload. Conversely, the other two conditions' parameters were significantly different from the in vivo condition for both preloads. The high preload results indicate that the ex vivo post-perfused and excised section conditions are both stiffer (47% both cases) and more viscous (23% and 87%, respectively) than the in vivo condition and that the ex vivo perfused condition is similar to the in vivo condition.

3.2. Large-strain creep indentation

Typical creep response and model fits for three indentations across all conditions for one representative liver are shown in Fig. 6. The in vivo and ex vivo perfused conditions show a consistent response for repeated indentations. Conversely, both unperfused conditions show permanent deformation as well as stiffening and a decrease in viscosity with repeated indentations. Table 1 reports the mean and standard deviations of changes in indentation characteristics between pairs of successive indentations within 18 min of each other across three conditions including results from the independent unperfused test (Fig. 7). These characteristics are represented in terms of differences in permanent deformation (Δ_i, the difference in the indenter's initial contact with the surface as compared to the first indentation), depth of indentation (Δ_D), and nominal steady-state strain (Δ_{ss}). The results show that the in vivo and ex vivo perfused conditions were statistically indistinguishable from each other for both loads with the exception of steady-state strain in the 100 g case ($\Delta_i p_{20\,g} = 0.30$, $p_{100\,g} = 0.33$; $\Delta_D p_{20\,g} = 0.96$, $p_{100\,g} = 0.20$; $\Delta_{ss} p_{20\,g} = 0.10$, $p_{100\,g} = 0.04$). In contrast, the post-perfused condition showed an inconsistent response with repeated indentations, including 11.9% permanent strain deformation, 7.2% difference in indentation strain, and 4.6% difference in steady-state nominal strain. The results from the independent unperfused test are similar to the post-perfused results with a 15% permanent strain deformation, 5% difference in indentation strain, and 10% difference in steady-state nominal strain.

To compare the variability in the liver time scales and amplitudes between indentations and across conditions, the means and standard deviations of the model parameters (τ_1, τ_2, A_0, A_1, A_2) for pairs of sequential indentations were calculated and are shown in Fig. 8. Again, the parameters for the in vivo and ex vivo perfused conditions were similar to each other and

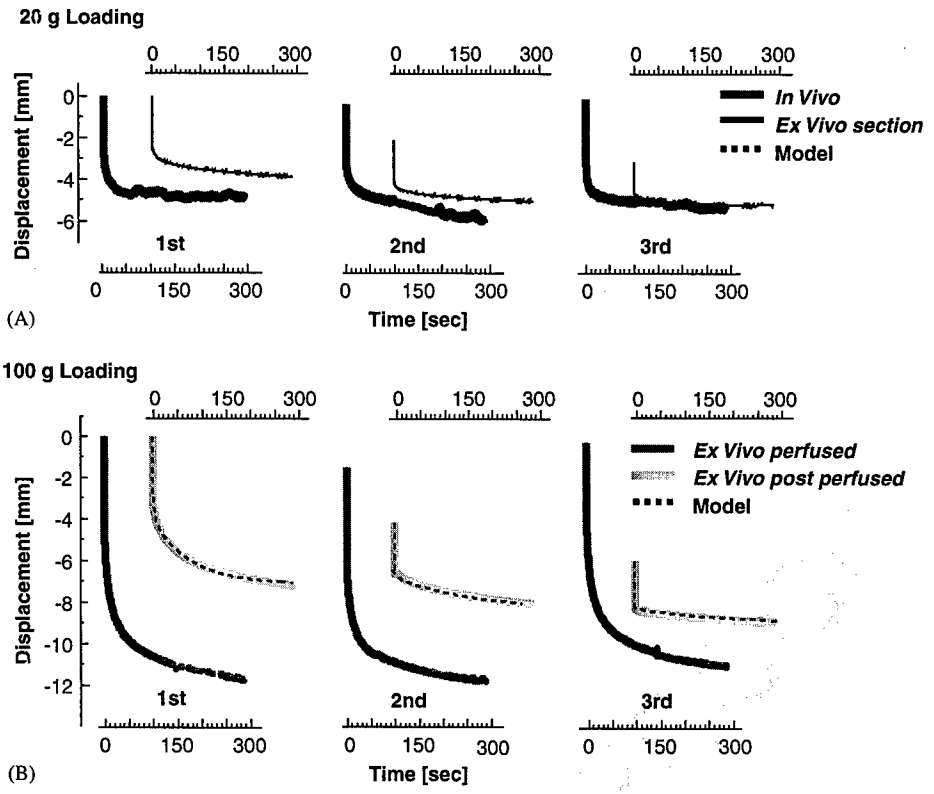

Fig. 6. Typical creep data for three indentations from one porcine liver for all four conditions. The top plot compares indentations between the in vivo response (90 min between the first and last indentation) and the in vitro response (30 min between the first and last indentation) under a 20 g load. The bottom plot compares indentations between the ex vivo perfused (78 min between the first and last indentation) and ex vivo post-perfused (30 min between the first and last indentation) responses under a 100 g load. The initial ramp and second-order model fits to the in vivo, ex vivo perfused, and ex vivo post-perfused indentations are plotted as dotted lines.

Table 1
Means ± SD of the differences observed in the indentation characteristics for pairs of successive large-strain creep indentations across three conditions including the independent unperfused test

	Condition	No. of pairs	Δ_i, mean initial contact strain (±SD)	$\Delta_D = D_1 - D_2$, mean indentation strain (±SD)	Δ_{ss}, mean steady-state strain (±SD)
20 g	In vivo	4	0.008 (0.008)	0.016 (0.009)	−0.021 (0.013)
	Ex vivo perfused	4	−0.001 (0.023)	0.015 (0.016)	0.015 (0.032)
100 g	In vivo	4	0.042 (0.035)	0.036 (0.020)	−0.043 (0.021)
	Ex vivo perfused	5	0.043 (0.081)	0.014 (0.015)	−0.039 (0.088)
	Ex Vivo post perfused	4	0.119 (0.031)	0.072 (0.031)	−0.046 (0.031)
	Independent ex vivo unperfused	1	0.150	0.050	−0.100

consistent with repeated indentations under both loads. The mean values for τ_1 and τ_2 are 1.86 ± 1.03 and 51.3 ± 18.0 s, respectively, with similar weights on the order of 0.08 for the 20 g load and 0.026 for the 100 g load. The value of A_0 was 0.239 ± 0.078 and 0.466 ± 0.083 for the 20 and 100 g loads, respectively. The ex vivo post-perfused condition had a consistent value for τ_1 between indentations ($p = 0.283$) that was also statistically indistinguishable to the in vivo case ($p = 0.603$). The rest of the parameters suggest that this condition is either not repeatable, not comparable to the in vivo case, or both.

The initial displacements of all trials were zeroed, and the means of each condition were compared at every point in time to evaluate the overall shape of the large-strain creep response. Fig. 9 shows means and the standard deviation of the means for the responses for the three conditions tested. The results show that the ex

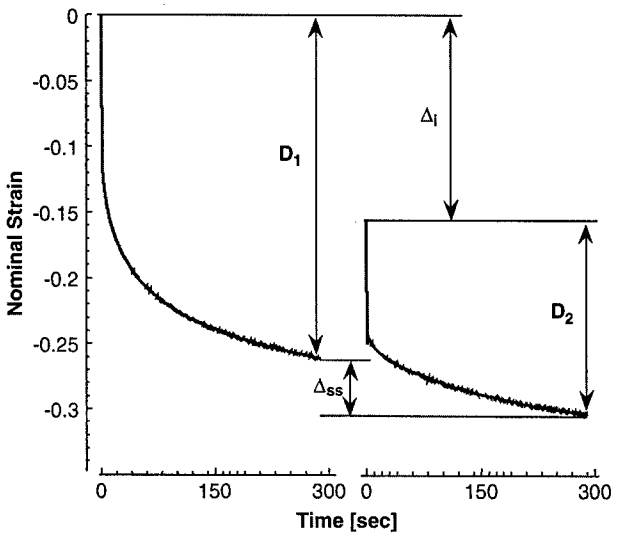

Fig. 7. Definitions of measures for characterizing differences observed between successive large-strain creep indentations, shown on a representative plot of data from a pair of ex vivo post-perfused indentations. Δ_i is the change in the initial point of contact with the surface (permanent deformation), Δ_D is the difference in depth of indentation (D_1-D_2), and Δ_{ss} is the difference in nominal steady-state strain.

vivo perfused condition closely approximated the in vivo condition with $p = 0.70$ at all times in the 20 g loading condition. Similarly, $p = 0.40$ for times greater than 27 s in the 100 g loading condition. The ex vivo post-perfused response is significantly different from the in vivo case with $p = 0.006$ for times greater than 22 ms. Lastly, strain hardening was observed in the in vivo and ex vivo perfused conditions since increasing the load by a factor of five doubled the mean steady-state response.

3.3. Histology

The analysis of the histology specimens from the three livers indicates that the structural integrity of the tissue was maintained over time in the experimental states compared to the control states. On a scale of 0–4, where 0 indicates no observed changes and 4 indicates severe changes, the mean score was between 0 and 1.7 across all conditions, time (5 h), and features. Some minimal changes were noted in the cytoplasm beyond 2 h into the perfused case and in the nonperfused conditions. It was also noted that the ex vivo perfused samples experienced some cellular contraction, contrasted with the cellular swelling seen in the in vitro excised sections. Minimal cell death was observed.

4. Discussion

This study presents a standard method for testing whole organs that produces repeatable results that can

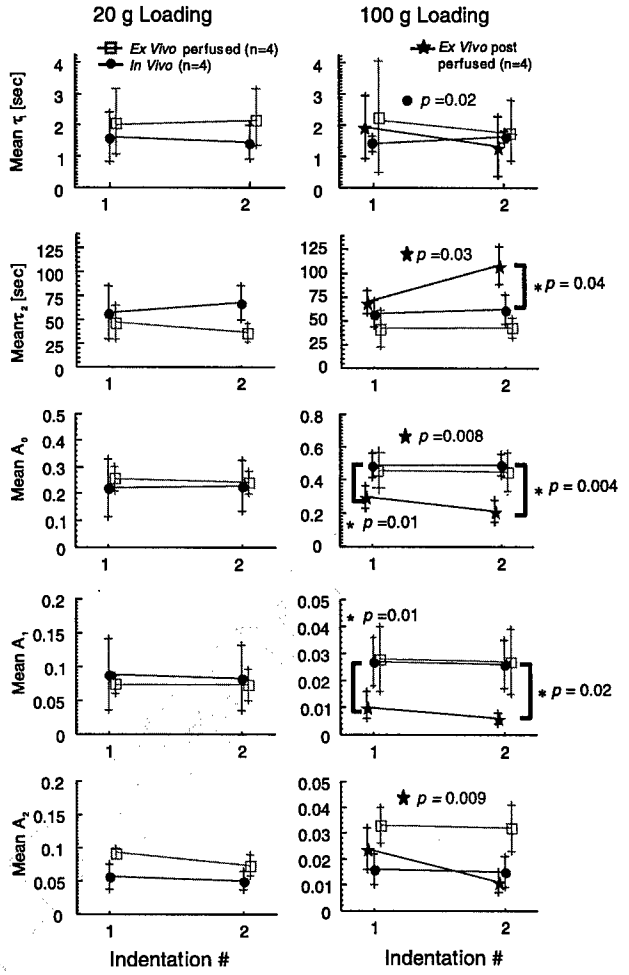

Fig. 8. Mean and SD of the creep model parameters (τ_1, τ_2, A_0, A_1, and A_2) for sequential indentations under both loads across the in vivo, ex vivo perfused, and ex vivo post-perfused conditions. p-values with a symbol denote a significant difference between indentations for that condition and an asterisk (*) denotes a significant difference compared to the in vivo case for a particular indentation.

be mathematically modeled to capture the realistic behavior of soft tissues. We built an ex vivo perfusion system that controls the perfusate, perfusion pressure, temperature, and surface hydration. Our results suggest that both geometric and physiologic boundary conditions must be considered when characterizing well-vascularized, solid, whole organs. Specifically, the elastic and viscous properties of liver are affected by perfusion as measured by both small-strain frequency response and large-strain creep indentation tests. The small-strain frequency tests show that both unperfused conditions were stiffer and more viscous than the in vivo condition under high preloads. The large-strain creep device showed permanent strain deformation for successive indentations for the post-perfused ex vivo tissues. The new perfusion system allowed for nearly in vivo results using both instruments in a controlled ex vivo setup.

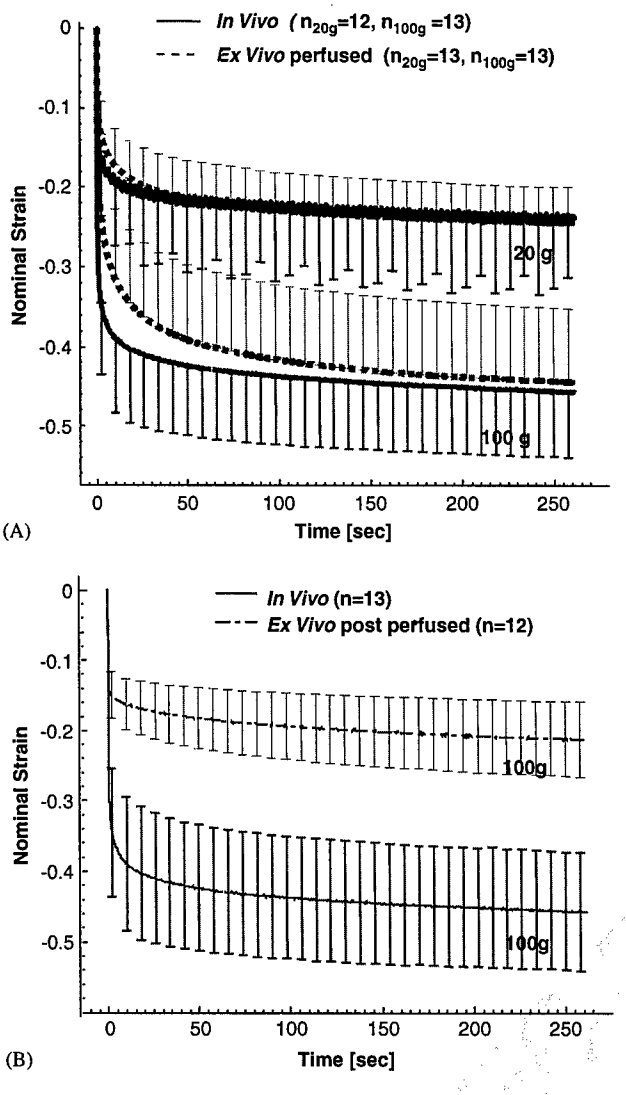

Fig. 9. (A) Mean nominal strain ± SD of the means versus time for the in vivo and ex vivo perfused creep data sets. The upper SD is shown for the ex vivo perfused and the lower SD for the in vivo. (B) Mean nominal strain ± SD of the means versus time for the in vivo and ex vivo post-perfused creep data for the 100 g tests.

The ex vivo perfused tissues exhibited similar viscoelastic behavior to the in vivo tissues and showed consistency (less than 4% strain differences) between successive indentations.

The results obtained here enlarge upon previous work on in vivo and ex vivo soft tissue material properties. While direct comparisons are not straightforward, the results of Brown et al. (2002, 2003) qualitatively support our observation that the liver is stiffer ex vivo than in vivo. They also note that the in vivo condition had more recovery between indentations than did the ex vivo. Gefen and Margulies (2004) made indentation measurements (strain < 20%) in three locations in porcine brains in both the in vivo and ex vivo states to compare the effects of perfusion. They reported that perfusion did not make a significant difference in material property identification. Brain tissue is nearly homogeneous, however, and does not hold the same volume fraction of blood as the liver. Thus the effects of perfusion on the viscoelastic properties of tissue are likely organ dependant. Although Dokos et al. (2000) and Gefen and Margulies (2004) tried to provide more realistic conditions for their ex vivo samples by controlling for external hydration and temperature, no one has made mechanical measurements on perfused ex vivo organs.

Many researchers "precondition" their ex vivo tissue samples with cyclic loading to obtain a steady-state response (Brouwer et al., 2001; Dokos et al., 2000; Liu and Bilston, 2002). Although this may make sense to simulate the in vivo state for tissues that undergo cyclic deformations like the heart and tendons, our results suggest that preconditioning soft nonload-bearing unperfused tissues drives fluid from the tissue, changing its viscous characteristics and internal boundary conditions. Our results show both an increase in the stiffness and viscosity of the organ, and a permanent deformation with repeated indentation for the excised section and the ex vivo post-perfused condition. Conversely, the stiffness and viscosity remained consistent with repeated indentations for both the in vivo and perfused ex vivo conditions, demonstrating the need for preserving the physiological boundary conditions when making mechanical measurements.

To maintain the internal boundary conditions and mechanical viability of the liver post mortem for the time course of our tests, we designed a perfusion system for ex vivo organs based on organ transplant systems. It has been shown that cellular injury occurs within 60–240 min of warm ischemia time (Platz et al., 1997; Schon et al., 2001). Using normothermic perfusion systems as a bridge to transplant, researchers have been able to maintain the viability of livers for up to 72 h (Butler et al., 2002; Platz et al., 1997; Schon et al., 2001). For this study, we were not interested in maintaining liver function but rather its structural integrity. The consistency seen in this study with repeated indentations, the similarities to the in vivo condition, and the histology results showing minimal changes in cellular integrity suggest that our cold ischemic time did not cause cell damage and that the perfusion system preserved the mechanical viability of the liver for the 5 hour duration of our ex vivo testing.

Despite the similarities in the viscoelastic response of the liver in the in vivo and ex vivo perfused conditions, small differences were seen that motivate improvements to the system for future measurements. The ex vivo perfused condition was slightly stiffer, thicker, less viscous, and experienced cellular dissociation as compared to the in vivo condition. This suggests that there was a mismatch in perfusion pressures and perfusate concentration. More recent examination of the literature

on porcine physiology has shown that the perfusion pressure for the hepatic portal venous branch of the system is smaller than the value used in this study, which was based on human values (Rasmussen et al., 1999). Optimally, the perfusate pressures would be determined with presacrifice arterial and venous measurements. It may also be useful to include perfusates with plasma proteins or other blood mimicking products to better match the oncotic and viscous properties of blood.

To address the needs of surgical simulation, our goal is to develop a constitutive model of the whole liver. Successful modeling requires data from a known geometry, with known loading conditions and external constraints. This study shows that both geometric and physiologic boundary conditions must be controlled, and that these can be done concurrently. One remaining challenge is accounting for the initial stress state. Placing the organ on a hard surface induces stresses that are not present in the in vivo state, and these must be taken into account when developing a constitutive law. It would also be ideal to model the individual contributions of the various tissue constituents (capsule, parenchyma, vessels) in the context of the whole organ. However, the intimate connections of the vasculature and capsule throughout the parenchyma make this a near-impossible task. It may be possible to make measurements that emphasize one of the constituents over the others; e.g., we are developing internal testing devices to make measurements that do not directly involve the external capsule (Kerdok and Howe, 2003).

Quantitative analysis of the perfused creep data under large deformations typical of surgical manipulation suggests that at least two time scales (1.86 and 51.3 s for the 300 s creep test reported here) are needed to describe the viscous parenchymal response of the liver. Physical reasoning suggests that the two time constants are from movement of fluid in two distinct pathways: one is from the inherent viscosity of the cells and the free exchange of interstitial fluid in the liver parenchyma, and another is due to blood flow in the liver's microvasculature. In future studies, it may be possible to use the perfusion system to vary the perfusate pressure to tease out the viscoelastic effects from those due to the interstitial fluid and extracellular matrix and from those due to the blood and vasculature.

Lastly, although this study used noninvasive surface indentations to allow for quantitative comparisons of mechanical response across conditions, complete mechanical characterization will involve stresses and strain rates that will bring the organ to failure and induce impact injuries. The need for boundary condition control and the potential invasiveness of future tests will mandate the use of ex vivo testing that can nearly approximate the in vivo condition. Once the models are well established using animal ex vivo tests, we can turn to in vivo testing to determine the human parameter values for the models.

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NON-RIGID SOFT TISSUE TRACKING WITH THREE-DIMENSIONAL ULTRASOUND

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Aims: The primary focus of our research efforts is modeling the mechanical behavior of soft tissues for surgical simulation and virtual surgical environments. Our current tissue characterization approach combines traditional indentation testing with three-dimensional ultrasonic imaging. Estimates of complete deformation fields obtained through imaging are incorporated into an iterative finite-element modeling (FEM) scheme [1] to identify tissue-specific parameters of a physically-based nonlinear poro-viscoelastic constitutive law [2, 3]. Our preliminary work suggests that deformation fields obtained from traditional optical flow techniques [4, 5] suffer from prohibitively high levels of noise present in ultrasound images. To address this, we present a non-rigid motion tracking technique that combines local optical flow measurements with a deforming finite-element model to improve motion estimates in noisy datasets.

Methods: Characteristic force-displacement relationships are obtained from an indentation of porcine liver while imaging with 3D ultrasound (Philips SONOS 7500 Live 3D Echo, Philips Medical Systems, Andover, MA, USA), providing the ability to estimate the complete three-dimensional deformation field of the sample under indentation. Since good textural information is required for differential optical flow techniques, principal component analysis is used to quantify local textural content and provide confidence values associated with local motion estimates. A sparse set of local estimates of optical flow is computed in regions with high confidence values by a modified version of the Lucas-Kanade algorithm [5]. A finite-element model, reflecting tissue sample geometry, boundary conditions, and predetermined constitutive law parameters, is registered to the ultrasound volume and used to properly constrain and interpolate the sparse optical flow estimates. The resulting non-rigid tracking method relies on optical flow estimates in regions of significant texture, and on displacement estimates from FEM in regions without trackable features. In future work, we plan to implement the proposed approach in an iterative framework where the computed deformation fields are used to refine the estimates of the FEM constitutive parameters.

Results: We present preliminary results comparing deformation fields obtained from traditional optical flow methods of Horn and Schunck [4] and Lucas-Kanade [5] to those obtained from FEM-constrained optical flow. Tracking accuracy is evaluated on an indentation trial of porcine liver with embedded markers and synthetically generated motion scenes with varying levels of image noise. We demonstrate robustness of motion estimates in noisy datasets and reduced levels of multi-frame flow accumulation error.

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IDENTIFICATION OF NONLINEAR CONSTITUTIVE LAW PARAMETERS OF BREAST TISSUE

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INTRODUCTION

Breast pathology is manifested by changes in stiffness. A model capable of capturing large deformations characteristic of surgical and diagnostic procedures is needed for applications in elastography, tactile imaging, surgical simulation and planning. Several researchers have acquired *ex vivo* indentation data to 10% nominal strain on various pathologic breast tissue samples [1-3]. Although they all report a nonlinear force-displacement response, only Samoni et al [2] model the response using a nonlinear hyperelastic constitutive law in the form of a polynomial strain energy function. A more physically based model is needed to acquire the unique material parameters of breast tissue undergoing large strains (>30%) typical of medical manipulations [4]. Since the model reflects the tissue structure, we can identify how the specific contributions of the individual tissue constituents vary with mechanical response and pathologic state. In this abstract we present large strain indentation data from normal glandular and infiltrating ductal carcinoma breast tissue, and determine the parameters of a modified Arruda-Boyce hyperelastic model through an optimization technique.

METHODS

Test Apparatus and Experimental Procedure. A portable manually driven test instrument was used to acquire indentation force-displacement data in the operating room within 10 minutes after excision [3]. Data was collected from 4 mm and 6 mm diameter flat-ended cylindrical punches for one sample of normal glandular tissue (11x16x4.4 mm) and for three samples of infiltrating ductal carcinoma (IDC) (10-19 mm diameter, 3.8-4.6 mm thick). The force and displacement data were filtered using a 30 Hz second-order low-pass butterworth filter. Maximum forces were used to determine the end of the loading period and the derivative of force with respect to displacement was plotted against force to determine the initial contact with the tissue for the first indentation. The data was divided into bins of quarter-percentile nominal strains to determine the mean loading curve from multiple loadings.

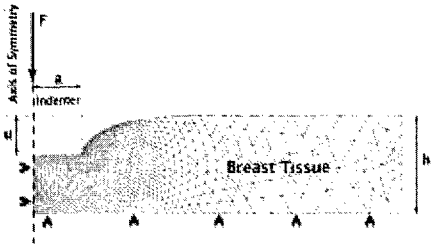

Figure 1: Mesh of axisymmetric indentation model, depicting tissue height *h*, indenter radius *a*, depth of indentation *u*, and applied force *F*.

Finite-element Modeling. Our indentation experiment is modeled as a two-dimensional, finite-deformation, axisymmetric problem, using commercial finite-element software (ABAQUS 6.4-1, HKS, Providence, RI). The mesh of the model consists of quadratic triangular elements (CAX6H), which were chosen over quadrilateral elements in order to improve the model's ability to deform to high nominal strains (Figure 1). The indenter, modeled as a rigid body with a flat-ended cylindrical shape and a 0.2 mm fillet radius with a frictionless contact, has a prescribed vertical displacement, and the corresponding reaction force is calculated. The bottom surface of the tissue is constrained in the vertical direction to account for testing on a hard substrate and has a frictionless boundary condition.

To model the large deformation behavior of breast tissue, a hyperelastic nonlinear constitutive model was chosen that accounts for the interactions among the various tissue constituent networks: collagen and elastin in parallel with a hydrated ground substance [5, 6]. In this study we focused on modeling the loading behavior of the material and neglected the dissipative component of the response. Thus, the nonlinear hyperelastic component of the model was used to capture the quasi-static loading response (50%/sec). Studies using the Arruda-Boyce hyperelastic model [1, 3], suggest that additional parameters are required to transform the 8chain network model designed for polymers into one that can be used for biological tissues.

An initial state of zero stress in the fibrous network cannot be assumed due to tissue hydration. Similarly, the resistance to hydrostatic deformations needs to be accounted for. Thus in addition to the initial shear modulus (μ) and the locking stretch (λ_L), we have added an initial network stretch (λ_0) to account for the pre-tensioned state of the fibrous network, and a bulk modulus (k) to account for three different mechanisms that contribute to changes in volume: resistance to flow from the interstitial fluid, resistance to osmotic pressure from the ECM network, and the inherent compressibility of the collagen network.

Parameter Identification. An iterative FEM technique is used to solve the inverse problem of identifying the parameters of the constitutive law, such that a satisfactory correspondence between model and experiment is obtained. Identification of the parameters is an optimization problem in four-dimensional parameter space [λ_0, λ_L, μ, K] where the objective function minimized is the mean squared error (MSE) between the modeled and experimental force vs. nominal strain curves. Since all of the parameters are directly related to physical constituents in the tissue, their upper and lower limits are well understood and a plausible parameter space can be defined [$1.0<\lambda_0<1.5$, $1.0<\lambda_L<2.0$, $10\ \text{Pa}<\mu<20\ \text{kPa}$, $100\ \text{kPa}<K<10\ \text{MPa}$]. Initially, this space is explored manually to estimate the sensitivity to each parameter and to obtain a physically feasible initial estimate for a given tissue type. A link between Matlab and ABAQUS environments carries out an iterative adjustment of material parameters, according to the Nelder-Mead simplex method. An iterative solution consisting of approximately 200 steps requires approximately 10 hours of computational time on a 3.0 GHz Pentium 4 machine with 2GB of RAM. The simplex method is seeded from three starting points to increase the likelihood of finding the global solution, rather than a local minimum. The optimization is carried out for both tissue types, with the termination conditions set to either a maximum of 1,000 iterations or the normalized simplex diameter smaller than $1\text{x}10^{-4}$.

RESULTS

The means and standard deviations of six indentations for the normal glandular tissue sample and 39 indentations for the IDC samples are shown in Figure 2. Also shown are the model responses reflecting the parameters obtained from the optimization using the initial set that produced the best fits (Table 1). The 5.5 and 4.5 fold increases in both initial shear and bulk moduli respectively and the decrease in the locking stretch, indicate that IDC is stiffer than normal glandular tissue. The small difference in the initial stretch suggests that this parameter is nearly independent of pathology.

DISCUSSION

This work is part of an ongoing effort in characterizing the nonlinear mechanical behavior of soft tissues. Here we show that a nonlinear hyperelastic constitutive model captures the effects of large strain (>30%) indentation on *ex vivo* breast tissues, and provides insight into the changes in tissue structure between pathologic states. We observed that large strains are needed not only to provide more realistic data for modeling medical manipulations but also to distinguish the differences in pathologic state.

The selected model serves to balance the swelling tendency of the hydrated ground substance with the tensile forces from the collagen network. Our exploration of the solution space demonstrated that the model's response was sensitive to changes in both the initial stretch and the locking stretch, and less sensitive to changes in the initial and bulk moduli. Since initial shear modulus is proportionally related to the bulk modulus and the stretches are inversely related, an increase in osmotic pressure should result in an increase in initial shear modulus

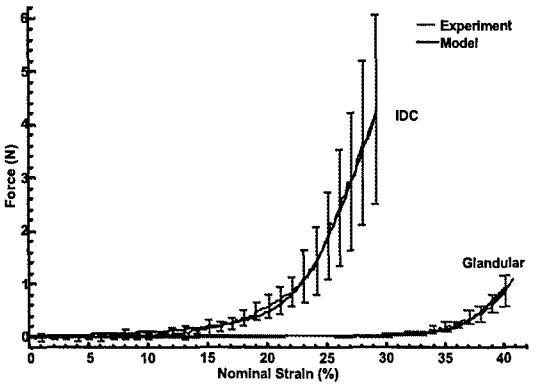

Figure 2: Loading curves (mean ± SD) and model fits for normal glandular and infiltrating ductal carcinoma tissue.

	λ_0	λ_L	μ [Pa]	k [MPa]	MSE
Normal (n = 6, a/h = 0.5)	1.017	1.114	49.62	1.488	0.0013
IDC (n = 39, a/h = 0.6)	1.014	1.036	274.6	6.680	0.0073

Table 1: Material parameters for constitutive model.

as well as a decrease in both stretches. Our results show that the restructuring of breast tissue from the normal to pathologic state involves a decrease in tissue compressibility (increase in bulk modulus related to water content, pH, and ion concentration) balanced by an increase in initial shear modulus and a decrease in the maximum extensibility (increase in number of cross-links) of the collagen fibrils. The initial stretch appeared to be unaffected by pathology.

While our optimization results produced excellent fits between model and experimental data, the issues of global convergence and uniqueness of solution need to be addressed in future work. Our initial optimization trials suggest that convergence to a global minimum is strongly dependent on a good initial estimate, motivating the need for a dense sampling of the parameter space, which could be interpolated to determine the initial estimate for the simplex method. Additionally, dense sampling would provide an overall understanding of the parameter space and help address the issue of uniqueness of the parameters found.

Future work will incorporate these new optimization techniques on additional data from Wellman [3] to the current model. The data includes both loading and unloading responses of breast tissue in five pathologic states. Thus the viscous term of the model will be reintroduced as in [5] to capture the observed hysteresis.

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3. Wellman, P. S., 1999, PhD Thesis, Division of Engineering and Applied Sciences, Harvard University, Cambridge, MA.
4. Liu Y., Kerdok A. E., Howe R. D., 2004, Second International Symposium on Medical Simulation, pp. 67-76.
5. Febvay, S., Socrate, S., 2003, Proceedings of IMECE'03, pp. 1-2.
6. Febvay, S., 2003, Master's Thesis, Massachusetts Institute of Technology.

Appendix B: selected CVs and BioSketches

Dawson, Steven L., M.D.

Howe, Robert D., Ph.D.

Ottensmeyer, Mark P., Ph.D.

Kerdok, Amy E., M.S

Petr Jordan, B.S.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Steven L. Dawson, MD	Program Lead, Medical Simulation, CIMIT

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
State University of New York at Buffalo	BA	1974	Biology
Tufts University	MD	1978	Medicine
Medical-Surgical Intern, Newton-Wellesley Hospital		1978-1979	
Radiology Residency, Massachusetts General Hospital		1979-1982	
Imaging and Interventional Radiology Fellowship, Massachusetts General Hospital		1982-1984	

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

A. Professional Experience.

Positions

1982-1986 Radiologist, Waltham Hospital
1986-1990 Radiologist, Lahey Clinic
1990-Present Interventional Radiologist, Massachusetts General Hospital
1997-1999 Director, New Initiatives, Center for Innovative Minimally Invasive Therapy
1998-1999 Director, Education, Center for Innovative Minimally Invasive Therapy
1998-Present Program Lead, Medical Simulation, CIMIT, Massachusetts General Hospital
1994-2001 Assistant Professor, Harvard Medical School
2000- Visiting Scientist, Massachusetts Institute of Technology
2001- Associate Professor, Harvard Medical School

Honors

1974 Phi Beta Kappa
1992 RSNA Exhibit: Lee MJ, Dawson SL, Mueller PR. Percutaneous management of periportal biliary malignancies with metallic endoprostheses: results, technical problems and causes of failure. Certificate of Merit Award.
1990 Associate Editor, *Seminars in Interventional Radiology*
1994 Member, American College of Radiology Expert Panel on Interventional Radiology of ACR Task Force on Appropriateness Criteria
1994 Fellow, Society of Cardiovascular and Interventional Radiology
1997- Examiner, American Board of Radiology Subspecialty Examination in Vascular and Interventional Radiology
1995- Corresponding Fellow, Cardiovascular and Interventional Radiology Society of Europe
1995 External Reviewer, Biomedical Programs, Battelle / Pacific Northwest National Labs
1999 Session Chair and Lecturer, US Public Health Service and National Cancer Institute Joint Working Group on Image Guided Diagnosis and Treatment

2000 Partners Excellence Award
2003 First Annual Edward M. Kennedy Award for Health Care Innovation
2004 Tenth Annual Satava Award for unique vision and commitment to bringing technology to medicine
2004 Army's Greatest Invention Award, Top Ten: VIRGIL Chest Trauma Training System
2004 Member, American College of Surgeons ad hoc committee on Simulators and Simulation for Surgical Education

B. Selected Publications, chosen from 64 peer-reviewed publications

Dawson SL, Rattner DW. "Minimally Invasive Therapies, Imaging and Energy Delivery Systems", in Strategies for the Future. The Role of Technology in Reducing Health Care Costs. Sandia National Laboratories, November, 1996, pp. 91-116.

Dawson SL, Kaufman JA. The Imperative for Medical Simulation. Proceedings of the IEEE 1998; 86 (3): 479-483.

Shaffer D, Meglan D, Ferrell M, and Dawson S. Virtual Rounds: simulation-based education in procedural medicine. In: Pien H, editor. Battlefield Biomedical Technologies, Proc. SPIE 1999; 3712:99-108 .

Cotin SC, Dawson SL. CAML: a general framework for the development of medical simulation systems. Proceedings of SPIE 4037: 294-300, 2000.

Dawson SL, Cotin S, Meglan D, Shaffer DW, Ferrell MA. Desigining a computer-based simulator for interventional cardiology training [with editorial]. Catheterization and Cardiovascular Interventions, 51; 522-528, 2000.

Dawson, SL. A critical approach to medical simulation. Bulletin of the American College of Surgeons, 2002; 87(11): 12-18.

Cotin S, Stylopoulos N, Ottensmeyer M, Neumann P, Rattner D, Dawson S. Metrics for Laparoscopic Skills Trainers: The Weakest Link! Dohi T and Kikinis R, eds. Proceedings of MICCAI 2002, Laboratory Notes in Computer Science 2488, 35-43, Springer-Verlag, Berlin. 2002.

Stylopoulos N, Cotin S, Dawson S, Ottensmeyer M, Neumann P, Bardsley R, Russell M, Jackson P, Rattner D. CELTS: A clinically-based computer enhanced laparoscopic training system. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press 336-342, 2003.

Manivannan M, Cotin S, Srinivasan M, Dawson S. Real-Time PC based X-ray Simulation for Interventional Radiology Training. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press, 233-239, 2003.

Kalanovic D, Ottensmeyer MP, Gross J, Dawson SL. Independent testing of soft tissue visco-elasticity using indentation and rotary shear deformations. Proceedings of 11th Annual Meeting, Medicine Meets Virtual Reality, Westwood JD, Hoffman HM, Mogel GT, *et al* eds. IOS Press, pp 137-143, 2003

Kerdok A, Cotin SM, Ottensmeyer MP, Galea AM, Howe RD, Dawson SL. "Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation," Medical Image Analysis, vol. 7, pp. 283-291, 2003.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Robert D. Howe, Ph.D.	Gordon McKay Professor of Engineering

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Reed College – Portland, OR	B.A.	1979	Physics
Stanford University – Stanford, CA	M.S.	1985	Mechanical Engineering
Stanford University – Stanford, CA	Ph.D.	1990	Mechanical Engineering

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Employment

1979-1981 Electronics Engineer, Kratos Display Systems. Los Gatos, CA.

1981-1983 Research Physicist, High Temperature Gasdynamics Laboratory, Stanford University

1984-1990 Research Assistant, Mechanical Engineering Dept. Stanford.

1990-1994 Assistant Professor of Mechanical Engineering, Harvard University.

1994-1997 Associate Professor of Mechanical Engineering, Harvard University.

1997-present Gordon McKay Professor of Engineering, Division of Engineering & Applied Sciences, Harvard University.

Selected Honors and Professional Service

National Science Foundation Young Investigator Award, 1993.

Best poster award, Sixth International Meeting of the Society for Minimally Invasive Therapy, Berlin (with William Peine), 1994.

Associate editor, *IEEE Transactions on Robotics and Automation*, 1994-1998.

Funding Review Panel Member, National Science Foundation, 1994, 2000.

Whitaker Foundation Biomedical Engineering Research Grant (career development award), 1995.

Chair and Organizer, Annual Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, ASME International Mechanical Engineering Congress and Exposition, 1996-1998 (with Susan J. Lederman).

Program Committee, International Symposium on Medical Robotics and Computer Assisted Surgery/MICCAI, 1994, 1995, 1997, 1998, 2000.

Program Committee, Frontiers of Engineering Symposium, National Academy of Engineering, Irvine, CA, Nov. 1998.

Selected Publications (from over 100 publications)

Samosky J, Burstein D, Grimson WE, Howe R, Martin S, Gray ML. Correlation of GAG distribution measured by dGEMRIC and spatially-localized mechanical stiffness in the human tibial plateau. *Journal of Orthopedic Research*, in press. (http://www.journals.elsevierhealth.com/periodicals/ortres/article/PIIS0736026604001202/fulltext)

M.P. Ottensmeyer, A.E. Kerdok, R.D. Howe, S.L.Dawson, "The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues," in S. Cotin and D.N. Metaxas, eds., *Proceedings of Medical Simulation: International Symposium - ISMS 2004*, Cambridge, MA, June 17-18, 2004, *Lecture Notes in Computer Science* vol. 3078, Springer-Verlag, pp. 9-18.

A.M. Galea and R.D. Howe, "Liver Vessel Parameter Estimation from Tactile Imaging Information," in S. Cotin and D.N. Metaxas, eds., *Proceedings of Medical Simulation: International Symposium - ISMS 2004*, Cambridge, MA, June 17-18, 2004, *Lecture Notes in Computer Science* vol. 3078, Springer-Verlag, pp. 59-66.

Y. Liu, A.E. Kerdok, R.D. Howe, "A Nonlinear Finite Element Model of Soft Tissue Indentation," in S. Cotin and D.N. Metaxas, eds., "*Proceedings of Medical Simulation: International Symposium - ISMS 2004*, Cambridge, MA, June 17-18, 2004, *Lecture Notes in Computer Science* vol. 3078, Springer-Verlag, pp. 67-76.T. Debus, T.-J. Jang, P. Dupont, and R. Howe, "Multi-Channel Vibrotactile Display for Teleoperated Assembly," International Journal of Control, Automation, and Systems 2(3):390-397, September 2004.

C.R. Wagner, S.J. Lederman, R.D. Howe, "Design and Performance of a Tactile Shape Display Using RC Servomotors," *Haptics-e* 3(4), August 2004.

T.J. Debus, P.E. Dupont, and R. D. Howe, "Contact State Estimation using Multiple Model Estimation and Hidden Markov Models," International Journal of Robotics Research 23(4–5):399-413, April–May 2004.

R.A. Beasley, R.D. Howe, and P.D. Dupont, "Kinematic error correction for minimally invasive surgical robots," Proceedings of the IEEE International Conference on Robotics & Automation, New Orleans, April 26-May 1, 2004.

R.L. Feller, C.K.L. Lau, C.R. Wagner, D.P. Perrin, R.D. Howe, "The Effect of Force Feedback on Remote Palpation," Proceedings of the IEEE International Conference on Robotics & Automation, New Orleans, April 26-May 1, 2004.

C.K.L. Lau, C.R. Wagner, and R.D. Howe, "Compliant Background Subtraction Algorithms for Tactile Rendering," Proceedings of the 12th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, Chicago, March 27-28, 2004, IEEE Computer Society Press.

J.W. Cannon, J.A. Stoll, S.D. Selha, P.E. Dupont, R.D. Howe, and D.F. Torchiana, "Port Placement Planning in Robot-Assisted Coronary Artery Bypass," *IEEE Transactions on Robotics and Automation* 19(5): 912-17, October 2003.

Cannon JW, Howe RD, Dupont PE, Triedman JK, Marx GR, del Nido PJ. "Application of robotics in congenital cardiac surgery," *Seminars in Thoracic and Cardiovascular Surgery - Pediatric Cardiac Surgury Annual* 6:72-83, 2003.

A.E. Kerdok, S.M. Cotin, M.P. Ottensmeyer, A.M. Galea, R.D. Howe, and S.L. Dawson, "Truth Cube: Establishing Physical Standards for Real-Time Soft Tissue Simulation," *Medical Image Analysis* 7(3):283-91, September 2003.

R. A. Beasley and R.D. Howe, "Tactile Tracking of Arteries in Robotic Surgery," Proceedings of the IEEE International Conference on Robotics & Automation, Washington, DC, May 11 - 15, 2002, pp. 3801-6.

T. Debus, T.-J. Jang, P. Dupont and R. Howe, "Multi-channel vibrotactile display for teleoperated assembly, Proceedings of the IEEE International Conference on Robotics & Automation, May 11 - 15, 2002, pp. 592-7.

C. R. Wagner, N. Stylopoulos, and R. D. Howe, "The Role Of Force Feedback In Surgery: Analysis of Blunt Dissection," in Proceedings of the 10th Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, Orlando, March 24-25, 2002, IEEE Computer Society Press, pp. 73-79.

S. S. Park, R. D. Howe, and D. F. Torchiana, "Virtual Fixtures for Robot-Assisted Minimally-Invasive Cardiac Surgery," in W. J. Niessen and M. A. Viergever, eds., Proc. Fourth International Conference on Medical Image Computing and Computer-Assisted Intervention – MICCAI 2001, Utrecht, The Netherlands, 14-17 October 2001, Lecture Notes in Computer Science Vol.1679, Springer, Berlin, p. 1419-20.

S. Selha ,P. Dupont, R.D. Howe, and D. Torchiana, "Optimal Port Placement in Robot-Assisted Coronary Artery Bypass Grafting," *Fourth International Conference on Medical Image Computing and Computer-Assisted Intervention*, Utrecht, The Netherlands, 14-17 October 2001.

Wellman, P.S, Dalton, E.P., Krag, D., Kern, K.A., Howe, R.D. "Tactile Imaging of Breast Masses: First Clinical Report," *Archives of Surgery* 136(2):204-08 Feb. 2001.

NAME	POSITION TITLE
Mark P. Ottensmeyer, Ph.D.	Lead Investigator, Simulation Group, CIMIT, MGH Instructor, Harvard Medical School

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
McMaster University, Hamilton, Ontario, Canada	B.Eng.Mgt	1994	Mechanical Engineering and Management
Massachusetts Institute of Technology, Cambridge, MA, USA	M.S.M.E.	1996	Mechanical Engineering
	Ph.D.	2001	Mechanical Engineering

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds two pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Research & Professional Experience

1991-1993 (summers) Research Assistant, McMaster University, Canada. Performed wind-tunnel experiments on electrical transmission line models to study transmission line galloping phenomenon. PI: Prof. Ozden F. Turan.

1993-1994 (summers) Research Assistant, Flexible Manufacturing Systems Laboratory, McMaster University, Canada. Developed power-up calibration system for AdeptOne industrial robot. PI: Prof. Hoda ElMaraghy.

1994-1996 Research Assistant, Human-Machine Systems Laboratory, M.I.T. Conducted research into and designed experiments on human performance in teleoperated surgery exercises with system time delays. PI: Prof. Thomas B. Sheridan.

1996-1998 Research Assistant, Haptics Group, Artificial Intelligence Laboratory, M.I.T. Developed thermal feedback device for virtual environment touch interface. PI: Dr. J. Kenneth Salisbury

1998-2001 Research Assistant, Haptics Group, Artificial Intelligence Laboratory, M.I.T. Developing minimally invasive surgical instruments for measuring mechanical properties of living organ tissues, performing in vitro and in vivo measurements. PI: Dr. J. Kenneth Salisbury

2001 Associate in Research, Harvard Medical School

2001-present Research Fellow, Massachusetts General Hospital

2001-present Instructor, Harvard Medical School

2001-present Lead Investigator, Simulation Group, CIMIT, Massachusetts General Hospital. Developing minimally invasive surgical instruments for measuring mechanical properties of living organ tissues, performing in vitro and in vivo measurements, designing simulators for medical/surgical training. P.I. Dr. Steven Dawson

Honors

1989 Ontario Scholarship
Sir Isaac Newton Physics Contest, Book award

1990 S.L. Squire Scholarship, McMaster University
Harry Lyman Hooker Scholarship, McMaster University

1991 Whidden Hall Residence Scholarship, McMaster University
Harry Lyman Hooker Scholarship, McMaster University

1992 Shell Canada Series Scholarship, McMaster University
Ray Lawson Scholarship, McMaster University

1993 Shell Canada Series Scholarship in Engineering and Management, McMaster University

Ray Lawson Scholarship, McMaster University
1994-'96 Post Graduate Scholarship A, National Sciences and Engineering Research Council, Canada (declined)
1996-'98 Post Graduate Scholarship B, NSERC, Canada
2003 Edward M. Kennedy Award for Health Care Innovation
2004 US Army's Greatest Invention Award 2003,
2004 Partners in Excellence Award

Society Memberships
Sigma Xi, The Scientific Research Society, Full Member, 1995-present
ASME, Associate Member, Associate Member, 1996-present

Publications
Refereed journal papers:
Ottensmeyer, Mark P. TeMPeST 1-D: an instrument for measuring solid organ soft tissue properties. Experimental Techniques, vol. 26, no. 3, 48-50, May/June 2002.
Kerdok, Amy E., Cotin, Stephane M., Ottensmeyer, Mark P., Galea, Anna M., Howe, Robert D., Dawson, Steven L. Truth Cube: Establishing Physical Standards for Real-Time Soft Tissue Simulation. Medical Image Analysis, vol. 7, 283-291, 2003.
Konofagou, Elisa E., Ottensmeyer, Mark P., Agabian, Sue, Dawson, Steven L., Hynynen, Kullervo. Estimating localized oscillatory tissue motion for the assessment of the underlying mechanical modulus. Ultrasonics, vol. 42, 951-6, 2004.
Kerdok, Amy E., Ottensmeyer, Mark P., Howe, Robert D. The Effects of Perfusion on the Viscoelastic Characteristics of Liver. Journal of Biomechanics, in press, 2005.

Conference papers:
Ottensmeyer, M.P.; Salisbury, J.K. Jr. In Vivo Data Acquisition Instrument For Solid Organ Mechanical Property Measurement. Proceedings of the Medical Image Computing and Computer-Assisted Intervention 4th International Conference, MICCAI 2001, Utrecht, The Netherlands, pp975-982. 14-17 Oct 2001.
Bruyns, Cynthia, Ottensmeyer, Mark. Measurements of Soft-Tissue Mechanical Properties to Support Development of a Physically Based Virtual Animal Model. MICCAI 2002. Proceedings of the Medical Image Computing and Computer-Assisted Intervention 5th International Conference, Tokyo, Japan, pp282-289. 25-28 Sept 2002.
Cotin, Stephane, Stylopoulos, Nicholas, Ottensmeyer, Mark, Neumann, Paul, Rattner, David, Dawson, Steven. Metrics for Laparoscopic Skills Trainers: The Weakest Link!. MICCAI 2002. Proceedings of the Medical Image Computing and Computer-Assisted Intervention 5th International Conference, Tokyo, Japan, pp35-43. 25-28 Sept 2002.
Kalanovic, Daniel, Ottensmeyer, Mark P., Gross, Joachim, Buess, Gerhardt, Dawson, Steven L. Independent testing of soft tissue visco-elasticity using indentation and rotary shear deformations. Proceedings of Medicine Meets Virtual Reality 11, Newport Beach, CA. IOS Press. pp137-143. Jan 22-25 2003
Stylopoulos, N., Cotin, S., Dawson, S., Ottensmeyer, M., Neumann, P., Bardsley, R., Russell, M., Jackson, P., Rattner, D. CELTS: A clinically-based Computer Enhanced Laparoscopic Training System. Proceedings of Medicine Meets Virtual Reality 11, Newport Beach, CA. IOS Press. pp336-342. Jan 22-25 2003

Other publications:
Ottensmeyer, Mark Peter. Telerobotic Surgery: Feedback Time Delay Effects on Task Assignment. Master's Thesis in Mechanical Engineering at the Massachusetts Institute of Technology. © M.I.T., 1996.
Ottensmeyer, Mark Peter. Minimally Invasive Instrument for In Vivo Measurement of Solid Organ Mechanical Impedance. Doctoral Thesis in Mechanical Engineering at the Massachusetts Institute of Technology, © M.I.T., 2001.

Amy Elizabeth Kerdok

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Cambridge, MA 02138
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web:http://hrl.harvard.edu/~kerdok/
Tel: (617) 308-2248
Fax: (617) 495-9837

Education

HARVARD UNIVERSITY

- Ph.D. in Engineering Sciences, Division of Engineering and Applied Sciences, — Cambridge, MA
- MIT/Harvard Health Science and Technology (HST) program in Medical Engineering/ Medical Physics, 1 year of medical coursework and 3 months of clinical clerkship — Expected 2005

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

- MS, Mechanical Engineering, Biomechanics focus — Cambridge, MA Sept. 1999

RENSSELAER POLYTECHNIC INSTITUTE

- BS, Biomedical Engineering (*summa cum laude)*; Concentration: Mechanical engineering; Minor: Management — Troy, NY May 1997

Research Experience

RESEARCH ASSISTANT: Harvard Biorobotics Laboratory; Soft Tissue Biomechanics — Cambridge, MA 2000-present

- Designed and constructed material property testing devices, finite element modeling of soft tissue behavior, clinical data collection and analysis
- Supervised and managed undergraduate projects in biomedical engineering: provided thesis guidance, helped with paper and presentation writing

RESEARCH ASSISTANT: MIT's Leg Laboratory and Harvard University's Concord Field Station; Sports Biomechanics — Cambridge, MA 1998-2000

- Experimental apparatus design and construction, human experimentation, data analysis, modeling the energetic and mechanical parameters of running

INTERN: Harvard Medical School's New England Regional Primate Center department of Cardiovascular Medicine with Dr. Stephen Vatner — Southboro, MA Summer 1994

- Assisted in open heart animal surgeries, ran animal experiments

Industrial Experience

PROJECT ENGINEER: ACT Medical Inc. (now TDC) — Newton, MA 2000

- Managed and co-managed team projects, designed and developed various medical products (concept, prototyping, testing, quality, manufacturing), wrote proposals, managed project budgets and timelines, customer relations, consultation

RESEARCH TECHNICIAN: Howmedica Inc. (now Stryker), Performance Engineering — Rutherford, NJ Summer 1995

- Operated MTS 810 and 407 controller single axis dynamic testing machines, designed orthopedic testing fixtures and molds (ISO, ASTM, and FDA standards)

Teaching Experience

HARVARD UNIVERSITY: Teaching Fellow — Cambridge, MA 2002, 2003

ES51 "Cornputer-Aided Machine Design"

- Developed and ran the laboratory curriculum to teach undergraduate students engineering design via SolidWorks and computer-controlled milling machines (using CamWorks), managed undergraduate teaching fellows

ES149 "Muscles, Reflexes, and Locomotion" — Spring 2001

- Conducted weekly review sections, graded problem sets

Leadership Experience

Select Committees and Elected Positions

- HST Medical Engineering/Medical Physics Admissions committee: read applications, conduct interviews, select incoming class of ~20 students (out of 200 applications) — 2001-2005
- HST Education for Professionalism, Ethics and Responsible Conduct in Science (EPERC's) Task Force: helped draft a plan to bring ethics and professionalism into HST courses, web research to apply for grant to make plan a reality — 2004-2005
- Student Representative for the Rensselaer Archer Center for Student Leadership: Organized Anderson Consulting Leadership conference — 1996
- Rensselaer Chapter of Pi Beta Phi Executive Board: Housing Committee Representative (worked with school to develop and fund a house for 60 women), Membership Chairman (developed alumnae database and semiannual newsletter) — 1995-1996

Mentoring

- HST Biomatrix Mentoring Program: Includes graduate and undergraduate biomedical engineering students, and members of industry and academia — 2002-2004
- Harvard College Science Mentoring Program for Women: graduate women in science are matched up with sophomore women — 2002-2003

Activities

- Harvard University Cycling Association: Team Captain (2003-4), Club President (over 100 members, raised $18k) and team MVP (2004), Collegiate National Championship Div 1 competitor (2002-4), organized 100 person fundraising ride — 2002-present
- Rensselaer Varsity Soccer, Most Dedicated, UCAA All-Academic team, Captain — 1993-1996

Computer Skills

- MATLAB, SolidWorks, CamWorks, ABAQUS (FEM), MS Visual Basic

Selected Awards & Honors

- Program Committee for International Symposium on Medical Simulation — 2004
- Keynote speaker for Hudson High School Graduation — 2003
- Faculty Achievement Award, Rensselaer Polytechnic Institute — 2003
- Harvard University Certificate of Distinction in Teaching — 2001-03
- Whitaker Fellowship, for advanced studies in Biomedical Engineering — 1997-03
- Livingston W. Houston Citizenship Award, Rensselaer Polytechnic Institute — 1997
- Paul B. Diach Award, top biomedical student, Rensselaer Polytechnic Institute — 1997
- Tau Beta Pi (national engineering honor society) — 1996
- Founder's Award for Excellence, Rensselaer Polytechnic Institute — 1995
- Rensselaer Alumni Scholarship — 1993
- Rensselaer Polytechnic Institute medal (mathematics and science scholarship) — 1992

Publications and Patents

Journal Articles

Kerdok, A. E., M. P. Ottensmeyer, R. D. Howe, 2005, "The Effects of Perfusion on the Viscoelastic Characteristics of Liver," Journal of Biomechanics, **in press**.

Kerdok, A. E., Cotin, S. M., Ottensmeyer, M. P., Galea, A. M., Howe, R. D. & Dawson, S. L. 2003. "Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation". Medical Image Analysis **7**, 283-91.

Kerdok, A. E., Biewener, A. A., McMahon, T. A., Weyand, P. G. & Herr, H. M. 2002. "Energetics and Mechanics of Human Running on Surfaces of Different Stiffnesses". Journal of Applied Physiology **92**, 469-478.

REFEREED CONFERENCE PAPERS

Kerdok, A.E., Howe, R.D., Characterizing large deformation behavior of liver for surgical simulation. In Proceedings of Biomedical Engineering Society Annual Meeting. Baltimore, MD, 2005 **(poster presentation).**

Jordan, P., Kerdok, A.E., Socrate, S., Howe, R.D., Breast tissue parameter identification for a nonlinear constitutive model. In Proceedings of Biomedical Engineering Society Annual Meeting. Baltimore, MD, 2005 **(poster presentation).**

Dollar, A.M., Kerdok, A.E., Diamond, S.G., Novotny, P.M., Howe, R.D., Starting on the right track: Introducing mechanical engineering with a project-based course on machine design. In Proceedings of ASME International Mechanical Engineering Congress & Exposition. Orlando, FL, 2005.

Kerdok, A.E., Jordan, P., Liu, Y., Wellman, P.S., Socrate, S., Howe, R.D., Identification of nonlinear constitutive law parameters of breast tissue. In Proceedings of ASME Summer Bioengineering Conference. Vail, CO, June 22-26, 2005. **(poster presentation)**

Kerdok, A.E.,Howe, R.D., A physical basis for a two time constant constitutive model for liver. In Proceedings of ASME Summer Bioengineering Conference. Vail, CO, June 22-26, 2005. **(poster presentation, won Honorable mention for PhD Student Poster competition)**

Kerdok, A. E., Socrate, S. & Howe, R. D. 2004. "Soft Tissue Modeling and Mechanics". In American Society of Biomechanics Annual Meeting 2004 (ed. M. Bottlang & S. M. Madey). Portland, OR. **(poster presentation)**

Ottensmeyer, M. P., Kerdok, A. E., Howe, R. D. & Dawson, S. L. 2004. "The Effects of Testing Environment on the Viscoelastic Properties of Soft Tissues". In Second International Symposium on Medical Simulation (ed. S. Cotin & D. Metaxas), pp. 9-18. Boston, MA: Springer Verlag. **(oral presentation)**

Liu, Y., Kerdok, A. E. & Howe, R. D. 2004. "A Nonlinear Finite Element Model of Soft Tissue Indentation". In Second International Symposium on Medical Simulation (ed. S. Cotin & D. Metaxas), pp. 67-76. Cambridge, MA: Springer Verlag. **(poster presentation)**

Kerdok, A. E. & Howe, R. D. 2003. "A Technique for Measuring Mechanical Properties of Perfused Solid Organs". In ASME Summer Bioengineering Conference. Key Biscayne, FL. **(poster presentation)**

Kerdok, A. E., Cotin, S. M., Ottensmeyer, M. P., Galea, A. M., Howe, R. D. & Dawson, S. L. 2001. "Truth Cube: Establishing Physical Standards for Real Time Soft Tissue Simulation". In International Workshop on Deformable Modeling and Soft Tissue Simulation (ed. E. Keeve). Bonn, Germany. **(oral presentation)**

CONTRIBUTED CONFERENCE PAPERS AND PRESENTATIONS

Kerdok, A.E., Howe, R.D., Dawson, S.L., Socrate, S., Mechanical characterization of liver for surgical simulation. Presented at Industrial Outreach Program. Harvard University, 2005 **(poster presentation).**

Kerdok, A. E., 2005, "Characterizing Large Deformation Behavior of Liver for Surgical Simulation," HST Forum, Boston, MA **(poster presentation).**

Kerdok, A. E., 2004, "The Effects of Testing Environment on Soft Tissue Properties," HST Forum, Boston, MA **(poster presentation).**

Kerdok, A. E., 2003, "Measuring Parenchymal Properties of Perfused Solid Organs," HST Forum, Boston, MA **(poster presentation).**

Kerdok, A. E., 2002, "Characterizing Soft Tissues for Surgical Simulation: Probing Parenchymal Properties," HST Forum, Boston, MA **(poster presentation).**

Kerdok, A. E., 1999, "Modeling the Effects of Surface Compliance on Running Biomechanics," HST Forum, Boston, MA **(poster presentation).**

THESES

Kerdok, A. E., 1999. "Energetics and mechanics of human running on surfaces of different stiffnesses". MS, Mechanical Engineering, Massachusetts Institute of Technology Cambridge.

PATENTS

Walczyk, D. F. & Kerdok, A. E. 2002. "Mechanical Weight Bearing Indicator for the Foot", pp. US 6,405,606 B1: Rensselaer Polytechnic Institute.

Petr Jordán

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7 Craigie Circle #23
Cambridge, MA 02138
(617) 864-1066

EDUCATION

- **Harvard University**, Cambridge, MA.
  Ph.D. candidate in Engineering Sciences. Division of Engineering and Applied Sciences.
  S.M. in Engineering Sciences. Division of Engineering and Applied Sciences, 2005.
  Medical Engineering and Medical Physics candidate,
  Harvard/MIT Division of Health Sciences & Technology.

- **Lipscomb University**, Nashville, TN.
  B.S. in Computer Engineering, minor in Pure Mathematics, Summa Cum Laude, 2002.
  Senior thesis: *Real-Time DSP Noise Cancellation for SQUID Biomagnetometers.*

RESEARCH

- Soft tissue mechanics.
  Advisor: Robert D. Howe, Harvard Biorobotics Laboratory.
  3D ultrasonic imaging, modeling and deformation tracking of soft tissue.
  (July 2003 – present)
- Real-time DSP-based noise cancellation for SQUID biomagnetometers.
  Advisor: Alan L. Bradshaw, Vanderbilt University, Department of Surgery.
  Signal processing, real-time system programming, circuit and cancellation coil design.
  (August 2002 – June 2003)
- Measurement of gastrointestinal magnetic fields with SQUID biomagnetomers.
  Advisor: Alan L. Bradshaw, Vanderbilt University, Department of Surgery.
  Signal acquisition and SQUID maintenance, investigation of the effects of diabetes on the biomagnetic activity of stomach and small intestine. (August 2001 – August 2002)

WORK

- **Research Assistant**, Biorobotics Laboratory, Harvard University
  (July 2003 – present)
- **Biomedical Engineer**, Department of Surgery, Vanderbilt University
  (June 2002 – June 2003)
- **Computer Assistant**, Information Services, Lipscomb University
  (August 1998 – May 2002)

TEACHING

Teaching Fellow, Introduction to the Mechanics of Solids, Spring 2005.
Division of Engineering and Applied Sciences, Harvard University.

PUBLICATIONS

Jordan P, Zickler T, Socrate S, Howe RD. "Non-Rigid Soft Tissue Tracking with Three-Dimensional Ultrasound." *4th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity.* Austin, TX, 2005.

Jordan P, Kerdok AE, Socrate S, Howe RD. "Breast Tissue Parameter Identification for a Nonlinear Constitutive Model." *BMES Annual Fall Meeting.* Baltimore, MD, 2005.

Kerdok AE, Jordan P, Liu Y, Wellman PS, Socrate S, Howe RD. "Identification of Nonlinear Constitutive Law Parameters of Breast Tissue." *Proceedings of the 2005 Summer Bioengineering Conference.* ASME, 2005.

Jordan P, Howe RD. "Identifying the Parameters of a Nonlinear Constitutive Law for Soft Tissue Using Three-Dimensional Ultrasound Imaging.", *Harvard/MIT HST Forum.* Boston, MA, 2005.

REFERENCE

Available on request.